Postpartum Haemorrhage
Defining Incidence and Modelling Risk Factors to Predict Different Thresholds of Blood Loss

Briley, Annette Lesley

Awarding institution:
King's College London

Postpartum Haemorrhage: Defining Incidence and Modelling Risk Factors to Predict Different Thresholds of Blood Loss

Annette Briley

A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

Florence Nightingale School of Nursing and Midwifery
King's College London

December 2013

Abstract

Background: Postpartum haemorrhage (PPH) remains a major cause of maternal mortality and morbidity, and in recent years there has been a temporal increase in the incidence of PPH and associated morbidities in resource rich countries. Individual risk factors for PPH have long been identified but the relative importance of each has been under explored and thus the potential for preventative strategies is unknown.

Aim: The aim of this study was to, i) ascertain the incidence of PPH at various thresholds in a South of England population, ii) identify the relative importance of predictor variables associated with PPH at different blood loss thresholds and iii) identify the independent and cumulative association of prepregnancy, pregnancy acquired and intrapartum variables on estimated blood loss following birth.

Methodology: A prospective observational study was undertaken in two maternity services. Estimated blood loss data for all women (n=10,213) were imported from NHS electronic summary records. A representative sample of cases (n=1897) was selected for review, using a weighted sampling strategy. Univariate analysis identified variables associated with mean estimated blood loss and PPH at various thresholds. Multivariate regression modelling assessed the association of sequentially acquired variables with PPH ≥500 ml, ≥1000 ml, and ≥1500 ml.

Results: The incidence of PPH ≥500 ml, ≥1000 ml ≥1500 ml ≥2000 ml and ≥2500 ml was 33.9% (95%CI 31.4 to 36.5), 9.4% (95%CI 8.5 to 10.4), 4.0% (95%CI 3.4 to 4.6), 2.0% (95%CI 1.6 to 2.4) and 0.8% (95%CI 0.7 to 1.0) respectively. Incidence of PPH ≥1000 ml was investigated by mode of birth. The incidence for spontaneous vaginal birth (SVD) was 4.75% (95%CI0.37 to 3.7)

and instrumental vaginal birth, 12.1% (95%CI 9.3 to 14.6). The incidence following abdominal birth was 18.2% (95%CI 15.8 to 20.7); elective CS 11.8% (95%CI8.9 to 14.5), emergency CS 22% (95%CI18.6 to 25.4). Multiple regression analyses identified different independent variables associated with overall PPH at different thresholds. Novel independent variables resulting from this study associated with PPH at varying levels, were Black African ethnicity (≥500 ml and ≥1000 ml) OR 1.68 (95%CI 1.23 to 2.28) and OR 1.50 (95%CI1.13to 1.98), assisted conception (≥500 ml) OR 3.80 (95%CI1.69 to 8.57), antenatal attendance feeling 'generally unwell' (≥500 ml) OR 2.03 (95%CI1.18 to 3.49), antenatal steroid administration for fetal reasons (≥1500 ml) OR 2.00 (95%CI 1.17 to 3.41). In addition some previously known variables were confirmed. These were the impact per unit of BMI (Kg/m^2) OR 1.04 (95%CI 1.01 to 1.04); previous PPH (≥500, ≥1000, ≥1500) 2.75 (95%CI1.40 to 5.44) 1.88 (96%CI 1.13 to 3.11) 2.39 (95%CI1.33 to4.28) multiple pregnancy (≥1000, ≥1500) 2.33 (95%CI1.23 to 4.41) 2.60(95%CI1.27 o 5.38) retained placenta (≥1000) 7.51 (4.08 to 13.8), interval to suturing (≥1000 ml) 1.74 (95%CI1.46 to 2.08). There was also a liner association with maternal temperature in labour and level of PPH.

Conclusion: This study found higher rates of PPH at all thresholds and, with all modes of birth. Which is not fully explained by rising Caesarean section rates. Prepregnancy and pregnancy acquired variables are commonly mediated through intrapartum events, and previous pregnancy management can impact on blood loss in subsequent pregnancies. Novel variables found in this study require further investigation, particularly the impact of Black African ethnicity, assisted conception techniques, antenatal steroid administration, and, feeling "generally unwell". Modifiable risk factors include preconceptual weight loss, expedient suturing of genital tract trauma and regular recording of maternal temperature in labour, which may alert staff to higher risk of PPH.

Acknowledgements

Firstly, I would like to thank my supervisors, Professor Jane Sandall and Dr Rachel Tribe, for their support. I would like to thank Professor Susan Bewley for her generous support at all stages and Professor Lucilla Poston for allowing me to pursue this within my work role, and for always being there with encouragement and advice.

Thanks to Paul Seed for providing statistical support and for his unending patience. And Dr Graham Tydeman for reviewing notes, ensuring consistency and providing independent advice, in addition to encouragement and support.

I am also grateful for the support of the team in the Division of Women's Health. Particularly Jenny Carter, with whom I have shared an office throughout the process, and Claire Singh. Both of whom kindly proof read this thesis, and Hiten Mistry and Karen Astrom, very special friends, who also read through this work. Special thanks to Hannah Powles for help with formatting.

Thanks to all my friends, who have shared this experience and always been there, and understood when I have dedicated time to my thesis.

But the biggest thanks go to my family: to Gary, for never doubting I would do this, and supporting me in every possible way. To Peter, Simon and Freya, for their love and encouragement. To Dotty, the dog, who has had fewer walks than is right for a Cocker Spaniel. To my Dad for always believing in me, and my cousin Janice Fixter, for making a doctorate look easy, and encouraging me to follow in her footsteps. Although there at the start, I am sad neither of you lived to see this day.

Table of Contents

List of Tables

List of Figures

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
APH	Antepartum Haemorrhage
ART	Assisted Reproduction Techniques
AMTSL	Active management of the third stage of labour
BMI	Body Mass Index
CEMACH	Confidential Enquiry into Maternal and Child Health
CI	Confidence Interval
CMACE	Centre for Maternal And Child Enquiries
CNST	Clinical Negligence Scheme for Trusts
CVP	Central Venous Pressure (line)
EBL	Estimated Blood Loss
CS	Caesarean Section
EU	European Union
FGM	Female Genital Mutilation.
FIGO	International Federation of Gynecology and Obstetrics.
g	grammes.
h	hours.
hh	hours, 24 hour clock
Hb	Haemoglobin.
ICD	International Classification of Disease codes
IOL	Induction of Labour.
IM	Intramuscularly.
IMD	Index of Multiple Deprivation.
ITU	Intensive Care Unit.
IU	International Units.
IV	Intravenously.

kg	kilogrammes.
l	litres
m^2	metres squared (as part of BMI measurement).
ml	millilitres.
m	minutes
mm	minutes, 24 hour clock
MOH	Major Obstetric Haemorrhage
MRP	Manual Removal of Placenta
NICE	National Institute of Health and Clinical Excellence
OC	Obstetric Cholestasis
OR	Odds ratio
PPH	Postpartum Haemorrhage
PTSD	Post Traumatic Stress Disorder
RCM	Royal College of Midwives.
RCOG	Royal College of Obstetricians and Gynaecologists
ROM	Rupture of Membranes
rFactor VIIa	Recumbent Factor 7a
SAMM	Severe Acute Maternal Morbidity
SVD	Spontaneous Vaginal Delivery
T°C	Temperature recorded in degrees Centigrade
TXA	Tranexamic Acid
UK	United Kingdom
UKOSS	United Kingdom Obstetric Surveillance System
USA	United States of America
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organisation

List of Abstracts and Publications Arising from this Thesis

Original Articles:

Briley A., Seed P.T., Tydeman G., Ballard H., Waterstone M., Sandall J., Poston L., Tribe R.M., Bewley S. 2014 Reporting Errors, Incidence and Risk Factors for Postpartum Haemorrhage (PPH) and Progression to Severe PPH: A Prospective Observational Study. *BJOG* 121, 876-88.

Abstracts:

Briley A., Seed P.T., Tydeman G., Waterstone M., Tribe R., Sandall J., Bewley S 2013. How much is too much? Unprecedented rates of PPH. NIHR Global Research Nurses Conference, London. Poster presentation

Briley A., Tydeman G., Seed P.T., Ballard H., Sandall J., Tribe R.M., Bewley S. 2013. Incidence and Risk Factors for Severe PPH: A prospective South East cohort study (STOP). Oral *poster British Maternal and Fetal Medicine Society Meeting*, Dublin. Poster presentation.

Briley A., Seed P.T., Ballard H., Tydeman G., Waterstone M., Tribe R., Sandall J., Bewley S. 2012. Unprecedented Rates of PPH: A prospective observational cohort study of blood loss in childbirth (STOP study). Oral *poster British Maternal and Fetal Medicine Society Meeting*, Newcastle. Poster presentation.

Briley A., Ballard H., Bewley S., Sandall J. 2011. The voice of experience: listening to the stories of PPH by women, their birth partners and the staff involved. *ICM Conference*. Durban, South Africa. **Oral presentation**

Briley A., Sandall J., Ballard H., Tydeman G., Tribe R., Bewley S. 2011. The voice of experience: listening to the stories of PPH for women, their partners and the staff involved (STOP study). Poster presentation British Maternal and Fetal Medicine Society Meeting, Harrogate

Briley A., Ballard H., Sandall J. 2009. Surveillance and Treatment of Postpartum Haemorrhage, can the prevention, prediction and management of PPH be improved? *Normal Birth Conference*, Grange Over Sands. **Oral presentation**

Oral Presentation:

Briley A., Seed P.T., Tydeman G., Sandall J., Bewley S. 2014. Postpartum Haemorrhage; risks, errors and incidence. ICM Conference, Prague. **Oral presentation.**

Chapter 1: General Introduction

General introduction

Pregnancy and birth are major life events and, in high resource countries, are rarely considered "risky", especially for the mother. In the UK maternal deaths have been reported since 1928 (Drife, 1997; RCOG, 1992). The system of confidential investigation into factors surrounding each maternal death has been admired and replicated in other high resource settings (Biaggi *et al*., 2004; Chichakli *et al*., 1999; Schuitemaker *et al*., 1998). There was a sharp decline in maternal deaths between 1935 and 1985 (RCOG, 1992), attributed to improvements in public health, the introduction of antibiotics and blood transfusion regimes and legislative changes, notably the Abortion Act (1967) (Drife, 1997). However the number of these untimely deaths has remained remarkably stable in recent years (Lewis, 2007). Causes and frequency vary in each triennium, but obstetric haemorrhage has been among the top 4 causes in every report.

With maternal death being a rare event in high income countries, severe adverse maternal morbidities have been identified as indicators of reproductive health, and a useful adjunct to maternal death statistics (Mantel *et al*., 1998; Waterstone *et al*., 2001; Hall, 2001; Pattinson and Hall, 2003; Brace *et al*., 2004; Say *et al*., 2004; Ronsmans and Filippi, 2004; Wen *et al*., 2005; Baskett and O'Connell, 2005; Brace *et al*., 2007; Callaghan *et al*., 2008). Moreover, maternal deaths are not representative of the major problems encountered every day in maternity services. In high resource settings postpartum Haemorrhage (PPH) seldom

results in maternal death, but is a major cause of serious morbidity (Lewis, 2007; Knight, 2007).

The UK has pioneered improvements in obstetric care, including maternal mortality statistics, clinical audit and the introduction of the United Kingdom Obstetric Surveillance System (UKOSS) to describe the epidemiology of uncommon disorders of pregnancy (Knight *et al*., 2005). Yet, with the exception of the Confidential Scottish Audit (Brace *et al*., 2004), there are no local, regional or national systems to record adverse events, identify exemplar or substandard care, and address issues contemporaneously. The UKOSS methodology, whilst effective for rare conditions, is not transferrable to common events, like PPH (Knight *et al*., 2005). This is due not only to the increased burden for clinical staff that data collection would incur, but also the anonymised, minimal data used. Whilst maintaining confidentiality, identification of specific areas of good or poor practice cannot be achieved.

The consequences of failing to prevent excessive blood loss following childbirth have been documented through the ages. Around 1500BC the Ebers Papyrus advocated the use of fly excrement, juniper berries, celery in milk or hemp in honey to stop bleeding (Nunn, 1996). Discovery of the original uterotonic drug, ergot, is attributed to herbalist Adam Lonicer in 1582. It was introduced into obstetrics in the 19th century to expedite labour, but caused fetal hypoxia and demise. However its effectiveness at preventing PPH when administered immediately post birth was noted (Stearns, 1822). By the late 19th and early 20th centuries numerous scientists were developing more sophisticated products, facilitating dose titration and reducing side effects. Initial clinical trials were undertaken in 1932 (Moir, 1962). But the identification of the structure of oxytocin and production of it in synthetic form in the 1950s revolutionised potential prophylaxis and treatment of PPH (Du Vingneaud *et al*., 1954).

Mechanical interventions have also been devised to prevent and treat PPH. These include uterine massage, bimanual compression and uterine packing.

Uterine massage has been advocated as an effective method of reducing blood loss and advocated in resource poor settings (WHO, 2006). A systematic review assessed the its' effectiveness following birth and before or after placental delivery to reduce blood loss and associated morbidities and mortalities (Hofmeyr *et al*., 2008). This review included one trial where 200 women were randomised to uterine massage or no uterine massage following active management of the third stage of labour (Abdel-Haleem *et al*., 2006). Blood loss exceeding 500 ml was rare, with wide confidence intervals (Relative Risk 0.52 95%CI 0.16 to 1.67), so interpretation is not possible. Whilst mean blood loss was less in the uterine massage group, as was the requirement for additional uterotonic drugs, the size of the study was a significant limitation, from which it was not possible to make recommendations.

Since completion of my study a further systematic review has included an additional RCT involving almost 2000 women (Hofmeyr *et al*., 2013). This study demonstrated disparity in the results by Centre, attributed to procedural differences, but concluded that uterine massage was less effective than intramuscular oxytocin with or without uterine massage (Abdel-Haleem *et al*., 2013). The Cochrane Review concluded there should be no revision of recommendations and highlighted the need for more trials as, if proved effective, uterine massage could be a simple inexpensive intervention that would save lives (Hofmeyr *et al*., 2013).

Bimanual compression has been advocated as an effective first-line treatment for PPH, despite no published data confirming its' efficacy (Winter *et al.,* 2007) there

remains general professional consensus supporting its use (RCOG, 2009). The widely used training algorithm 'HAEMOSTASIS' includes bimanual compression, as shown in Figure 1 (Chandraharan and Arulkumaran, 2005).

H	Ask for help
A	Assess (vital parameters, blood loss) and resuscitate
E	Establish etiology, ensure availability of blood, ecbolics (Syntometrine, ergometrine, bolus oxytocin)
M	Massage uterus
O	Oxytocin infusion/prostaglandins – IV/per rectal/IM/ intramyometrial
S	Shift to operating theatre – exclude retained products and trauma/bimanual compression
T	Tamponade balloon/uterine packing
A	Apply compression sutures – B-Lynch/modified
S	Systematic pelvic devascularization – uterine/ovarian/quadruple/internal iliac
I	Interventional radiologist – if appropriate, uterine artery embolization
S	Subtotal/total abdominal hysterectomy

Figure 1.1: HAEMOSTASIS mnemonic advocated by Chandraharan and Arulkumaran, 2005.

No additional work regarding the efficacy of bimanual compression has been published since undertaking the current study, but the HAEMOSTASIS mnemonic, shown in Figure 1.1, is advocated as a logical progression through procedures and has been associated with fewer blood transfusions, peripartum hysterectomies and maternal mortality (Varatharajan *et al.,* 2011).

Uterine packing, most commonly with gauze, was described in early obstetric textbooks (Cosgrove, 1936). By the 1950s this technique became less popular due to concerns about the pack inhibiting uterine contraction and potential infection, despite no evidence of either (Hester, 1975). Balloon tamponade, initially with a Foley catheter, preceded the development of the Bakri balloon (in 2001) and similar devices, which when inflated (to a maximum of 500ml) provides pressure but has a tip that enables drainage, therefore negating the possibility of a concealed Haemorrhage (Bakri *et al.,* 2001).

Since undertaking the work for this thesis developments in military medicine have led to the availability of locally applied haemostatic agents, for example Chitosan, the effectiveness of these have been reported in cases of severe PPH (Schmid *et al*., 2013). These interventions appear promising as packing with a haemostatic agent may reduce bleeding locally whilst simultaneously providing time for uterotonic drugs to take effect (Schmid *et al*., 2012). Additionally a retrospective case series investigating the utility of transabdominal uterine packing with gauze in cases of central placenta praevia, reported avoiding hysterectomy in 93% of cases (Ge *et al*., 2012), compared with the 84% overall success rate reported in the literature (Douchmouchtsis *et al*., 2007). These rates in a single Centre may be attributable to operator competence, unit protocols and other interventions to reduce blood loss, which are not described in the paper (Ge *et al*., 2012). However with reported increasing rates of abnormal placentation these findings require further investigation.

Uterine compression sutures were first described in a small series of 5 cases in 1997 (B-Lynch *et al.,* 1997). Since that time various modifications of this technique have been described, but similarly these have been relatively small case series (Cho *et al.,* 2000; Hayman *et al.,* 2002) A review suggested that compression sutures were a simple treatment for intractable bleeding less mutilating to the woman than hysterectomy (El-Hamamy and B-Lynch, 2005)

Reduction of pulse pressure to that of venous flow, enabling haemostasis through clot formation is the rational behind internal iliac artery ligation, which was developed in the early part of the 20th century to control PPH. Although success rates were not specified, the procedure was described as "effective" or "very effective"(Clark *et al.,* 1985). In the 1980s a case series reported efficacy ranging from 25-40% (Clark *et al.,* 1985). More recently a series of 117 cases in a single centre over a 15 year period reported a 100% success rate, but only 37 were

obstetric cases and uterine conservation was achieved in only 13 of these (Papp *et al.,* 2006). There are currently no randomized controlled trials comparing internal iliac artery ligation with any other techniques to arrest bleeding (Shah and Wright, 2009).

Uterine artery ligation was fist described to arrest PPPH in 1966 (O'Leary and O'Leary, 1966). By ligating the uterine arteries at the level of the cervical os the blood flowing to the uterus was dramatically reduced, rendering this particularly useful when treating PPH caused by atony or abnormal placentation. Initial fears that future pregnancies may be compromised by this treatment have proved unfounded, but complications identified in a recent systematic review included arterial injury, haematomas and nerve ischaemia have been reported (Doumouchtsis *et al*., 2007).

Arterial embolisation as a treatment to control PPH was first used in two cases and published in 1980 (Pais *et al*., 1980). Since that time it has used successfully to control PPH (Doumouchtsis *et al*., 2007). It is particularly useful when excessive bleeding is anticipated (in cases of abnormal placentation for example) and the intra-arterial catheters can be placed in situ prior to delivery. The unpredictable nature of PPH and the necessity for the patient to be stable for transfer to a radiology suite is a limiting factor for this treatment, although a recent report using national data reported a dramatic increase in the use of arterial embolization in Korea (Cho *et al*., 2013)

Peripartum hysterectomy remains the ultimate treatment for uncontrollable Haemorrhage. The incidence of this is variably reported, as indicated in Tables 1.1a and 1.1b, although this not an exclusive list, and definition variations are

highlighted in the table footnote. Of those reviewing emergency peripartum hysterectomy rates over time, several report increased incidence in more recent years (Parazzini *et al.,* 2013; Bodelon *et al.,* 2009; Flood *et al.,* 2009). A recent review article reported the incidence of emergency peripartum hysterectomy (EPH) as 0.24 to 8.9 per 1000 births (Machado, 2011).

Table 1.1a: Incidence of emergency peripartum hysterectomy as reported in the literature before the current study

Authors publication date	Type of study, sample size (n)	Country	Timeframe for studies	Incidence of EPH per 1000 births
Glaze *et al*., 2008	Retrospective case review, (87)	Canada	1999-2006	0.8
Eniola *et al*., 2006	Retrospective case control study, (22)	UK (South east England)	1997-1998	0.45
Bai *et al*., 2003	Retrospective case control study, (54)	Korea	1986-2001	0.045
Selo-Ojeme *et al*., 2005	Retrospective case control study, (15)	UK (London)	1993-2003	0.48
Bakshi & Meyer, 2000	Retrospective case review, (39)	USA (New York)	1990-1995	2.7
Bodelon* *et al*., 2009	Population based, case control, (896)	USA (Washington State)	1987-2006	0.56 (0.25 in 1987; 0.82 in 2006)
Casteneda *et al*., 2000	Retrospective case review, (217)	USA (Illinois)	1967-1995	NR
Chestnut** *et al*., 1985	Prospective case review, (117)	USA (Tennessee)	1963-1983	0.32
Choi*** *et al*., 2008	Retrospective case review (31)	Korea	1998-2006	0.05
Ding *et al*., 2006	Retrospective case review (8)	Taiwan	1998-2004	2.5
El Jallad *et al*., 2004	Retrospective case review (61)	Jordan	2001-2002	0.87
Engelsen *et al*., 2001	Retrospective case review	Norway	1981-1996	0.2

	(11)			
Erman Akar *et al*., 2004	Retrospective case review (38)	Turkey	1996-2001	0.26
Jou**** *et al*., 2004	Retrospective case review (287)	Taiwan	2002	0.013
Habek & Becarevic, 2007	Retrospective case review (17)	Croatia	1995-2003	0.078
Kastner *et al*., 2002	Retrospective case review (48)	USA (New York)	1991-1997	1.4
Kayabasoglu *et al*., 2008	Retrospective case review (28)	Turkey	2001-2007	0.37
Knight *et al*., 2007	Population based study (318	UK	2005-2006	0.4
Kwee *et al*., 2006	Nationwide registration (48)	Netherlands	2002-2003	0.33
Langdana *et al*., 2001	Retrospective case review (17)	Ireland	1990-1999	0.03
Yucel *et al*., 2006	Retrospective case review (34)	Turkey	1995-2003	0.29
Yamani Zamzami, 2006	Retrospective case review (17)	Saudi Arabia	1991-2002	0.5

*Bodelon *et al*., included CS performed up to 30 days post birth
**Chestnut *et al*., 73/117 PEH were considered "elective"
***Choi *et al*., only reported EPH associated with placenta praevia
****Jou *et al*., only investigated EPH in primiparous women

Table 1.1b: Incidence of emergency peripartum Haemorrhage as reported in the literature since the current study

Authors publication date	Type of study, sample size (n)	Country	Timeframe for studies	Incidence of EPH per 1000 births
Flood *et al*., 2009	Retrospective cohort study (358)	Ireland	1966-2005 1966-1975 1976-1985 1986-1995 1996-2005	0.4 0.85 0.44 0.2 0.2
Awan *et al*., 2011	Retrospective case review (33)	Australia	1999-2008	0.85
Abasiatti *et al*., 2013	Retrospective case review (28)	Nigeria	2004-2011	0.23
Bateman *et al*., 2012	Nationwide all payer hospital database review	USA	1994-1995 2006-2007	0.72 0.83
Chen *et al*., 2013	Single centre population based study (64)	China	2000-2010	0.02
Chibber *et al*., 2012	Retrospective case control study (59)	Kuwait	1983-2011	0.39
Christopoulos *et al*., 2011	Retrospective case study (15)	Greece	1994-2009	0.92
Demirci *et al*., 2011	Retrospective case review (39)	Turkey	2008-2009	0.37
Gurtani *et al*., 2013	Case series (41)	Iran	2004-2009	1.39
Jones *et al*., 2013	Retrospective case review (47)	UK (London)	2000-2011	0.85
Kara, 2012	Retrospective case review (54)	Turkey	2003-2009	1.87
Karayalcin *et al*., 2011	Retrospective case review (73)	Germany	2003-2008	0.63
Khan *et al*., 2012	Retrospective cross sectional study (218)	Pakistan	2000-2010	10.5
Jin *et al*., 2014	Case control study (21)	China	2005-2013	0.024
Lee *et al.,* 2012	Retrospective case review (46)	South Korea	2008-2010	2.28
Parazzini *et al*., 2013	Regional database review (905)	Italy	1996-2010	0.70
Zwart *et al*., 2010	Prospective nationwide population based cohort (205)	Netherlands	2004-2006	0.3

Prior to setting up the current study several reviews had shown distinct variation in the policies and practices regarding the prevention and treatment of PPH (Winter *et al.,* 2007; Knight, 2007). A more recent review also demonstrated persistent differences in management prior to peripartum hysterectomy (Rossi *et al.,* 2013).

Throughout the literature, the importance of recognising and accurately assessing blood loss following the birth of the baby has been identified as problematic and contributory to adverse outcomes (Drife, 1997; Lewis, 2003; Brace *et al.,* 2004).

Following the birth of the baby and placenta there is a normal blood loss from the internal surface of the uterus that settles as uterine contraction and involution occur. The volume constituting normal blood loss has long been the subject of debate (Gyte, 1992). Excessive blood loss following delivery, or postpartum Haemorrhage (PPH), is a common obstetric complication, reportedly affecting 1 in 10-100 women worldwide (Carroli *et al.,* 2008). Most PPHs occur within the first 24 hours following childbirth and are referred to as primary postpartum haemorrhage. Whilst uterine atony is acknowledged as a major cause of primary PPH (RCOG, 2009), it is estimated that 40% of women who experience PPH have identifiable risk factors (Ramanathan and Srulkumaran, 2006); therefore the majority of PPHs still occur unexpectedly. Many risk factors for PPH have been identified and variably reported. The current study aims to identify risk factors in a contemporaneous cohort with adequate resources to deal with PPH and to quantify the rate of blood loss at various thresholds.

Secondary postpartum haemorrhage is defined as excessive bleeding from the genital tract 24 hours to 12 weeks following childbirth (Arulkumaran *et al.,* 2009). The causes of secondary PPH are different to those for a primary PPH, and are most commonly due to sub-involution leading to failure to obliterate the large vessels caused by infection or retained products of conception (Neill et al, 2002). Secondary PPH has also been linked with genital tract infection, which remains a cause of maternal death in the UK (Lewis, 2007a). The incidence of secondary PPH is reportedly 2% in resource rich countries, but remains unknown in low income settings (Alexander, 2002).

The majority of available evidence regarding PPH relates to the incidence, management and outcomes associated with primary PPH.

This thesis focuses on primary PPH, investigating and improving methods of recording and reporting estimated blood loss, and the prediction of those at risk of PPH ≥500 ml, ≥1000 ml and ≥1500 ml.

Outline of the thesis

Chapter 2 Outlines the background leading up to the STOP study**.**

Chapter 3 highlights the methodological considerations involved in the design of the STOP study. While methods are described in the following chapter, the rationale for these is provided in detail here.

Chapter 4 describes methods used to undertake the STOP study and the aspects of it covered by this thesis

Chapter 5 describes the missing data and reporting errors between summary data on NHS electronic databases and documented in handheld maternity notes and other NHS reporting systems.

Chapter 6 describes the study population and the risk factors associated with mean estimated blood loss and estimated blood loss thresholds.

Chapter 7 describes the selection of variables to be used in regression models to identify risk factors for PPH.

Chapter 8 describes the construction of models to identify predictive variables for PPH ≥500, ≥1000 and ≥1500 ml.

Chapter 9 contains a general discussion of the findings, in light of other more recent findings. It also describes the limitations of the current study, and identifies implications for practice and areas for future research.

Having described the nature and size of the problem Chapter 2 describes the evidence base prior to the current study.

Chapter 2: Background

2.1 Introduction

As identified previously there is controversy around many aspects of PPH, from definition to estimation and assessment to of blood loss.

The aim of a literature review is to objectively present the current evidence/knowledge on a topic, and produce a summary based on previously published research (Bowling, 2009).

In recent years systematic literature reviews are advocated as the 'gold standard' used for close examination of specific topics, or to answer clearly formulated questions (White and Schmidt, 2005). By employing rigorous, explicit protocols at each step of the review process, reviewer bias is reduced and the process is replicable (Higgins and Green, 2008). However, this systematic approach is not without limitations, including: 1) ensuring the reviewers' methodological rigour and strength of the findings, prior to application to patient care; 2) systematic reviews are time consuming so it is possible for the conclusions to be superseded by new evidence prior to, or shortly after completion; 3) it is possible that a large well conducted randomised controlled trial provides more compelling evidence than a systematic review of small, underpowered trials.

In contrast narrative reviews utilise a variety of forms of evidence that may not conform to the rigid protocols employed in systematic reviews, for example they may be evidence based, but may not be research (Green, 2001; Bowling, 2009). These reviews critique and summarise a body of literature around a topic, and therefore have been advocated as more useful when investigating more broad literature around a subject as opposed to a specific, focused question or area of

investigation and potentially more appropriate for thesis (Griffiths and Norman, 2005; Cronin *et al.,* 2008).

The differences between systematic and narrative reviews are summarised in Table 2.1 (Cipriani and Geddes, 2003).

Table 2.1 Summary differences between systematic and narrative reviews (adapted from Cipriani and Geddes, 2003).

Systematic Reviews	Narrative Reviews
Investigate a clearly defined topic or question	Provide an overview of an area
Explicit, pre-specified search protocols are used to find literature	Explicit, pre-specified systematic literature search protocols are not used
Inclusion and exclusion criteria are specified in studies selected for review	Studies to support the reviewers' recommendations are not selected according to an explicit predetermined protocol
Data from a primary source may be synthesised in meta-analysis, individual studies may be "graded" for quality of evidence.	May use a grading system to assess the quality of individual studies.
Authors recommend further research in areas where evidence is lacking	Authors make recommendations based on opinions and experience when evidence is lacking. These recommendations may be graded based on the quality of underlying evidence.

Due to the extensive range of the literature around PPH, the abundance of literature in some aspects and paucity in others, combined with the lack of RCTs in the area, a narrative review was regarded as appropriate for the current study.

2.2 Literature search strategy

Initially electronic databases were searched:

AGRIS 1999 to 2004; Maternity and infant Care 1971 to March 2010; Medline In-Process & Other Non-Indexed Citations and Ovid Medline 1946 to present; Cochrane Library to present; PubMed; Web of Science; CINAHL; Embase Classic+ Embase 1947 to 2010 May 1; Global Health 1973 to 2010 Week 15. These dates were later extended to May 2014 to inform the discussion and include studies and reviews undertaken during and post this work.

International organisations websites and publications were reviewed, as they are all concerned with maternal morbidity and mortality. These included: World Health Organisation (WHO) (www.who.org), UNICEF (www.unicef.org), Save the Children (www.savethechildren.org.uk) and Maternity Worldwide (www.maternityworldwide.org.uk).

National and international professional and guideline groups were also investigated, these included:

Royal College of Midwives (RCM); International Confederation of Midwives (ICM); Royal College of Obstetricians (RCOG); Royal College of Anaesthetists (RCOA); Confidential Enquiry in to Maternal Deaths and Child Health (CEMACH); National Institute of Clinical Health and Excellence (NICE); United Kingdom Obstetric Surveillance Service (UKOSS); American College of Obstetricians and Gynecologists (ACOG); The Australian and New Zealand College of Obstetricians and Gynaecologists (ANZCOG); Institute of Medicine (IOM); Federation of Gynecologists and Obstetricians (FIGO); Scottish Confidential Audit of Severe maternal Morbidity; Cochrane Database of Systematic Reviews.

Other databases were searched for guidelines: UK, www.eGuidelines.co.uk; New Zealand www.cdhb.health.nz; USA www.cmqcc.org (California Maternal Quality Care Collaborative); Australia www.clinicalguidelines.gov.au, www.health.qld.gov .au (Queensland), www.sahealth.sa.gov.au (South Australia), www.thewomens.org.au (Melbourne); Europe www.

Initial key words were: postpartum haemorrhage, postpartum hemorrhage, obstetric haemorrhage and obstetric hemorrhage.

Non-English publications were excluded. When randomised controlled trials were reviewed, papers where the population, intervention, comparison group or outcome (PICO) was not clearly described were also excluded.
Review data were selected to investigate PPH in high, middle and low resource countries, and some combinations of mixed resource settings. Similarly review data were selected where particular interventions, policies or practices were compared.

Following the basic search for PPH other search terms were added to identify and investigate a range of literature around this common obstetric complication. In all cases haemorrhage was spelt with and without the 'a'.

To investigate definitions, key words included: minor PPH; severe PPH; major PPH; massive obstetric haemorrhage; major obstetric haemorrhage; MOH; definitions; classification; life threatening.

To investigate measurement, key words included: blood loss; childbirth; measure; measurement; assess; assessment; estimate; estimation; gravimetric; visual; drapes; biochemical; weigh; weight.

To investigate pre-existing risk factors, key words added included; ethnicity; ethnic minority; BME; Hispanic; Black; Caucasian; Chinese; immigration; immigrant; social exclusion; access to care; index of multiple deprivation; age; old; older; teenage; young; younger; obesity; overweight; lean; underweight; heavy; Body Mass Index; BMI; parity; previous C(a)esarean section; previous PPH; fibroids; endometriosis, assisted conception techniques; IVF; GIFT; ovarian stimulation; endometriosis; polycystic ovary syndrome; PCOS; metabolic syndrome; late booker; late booking; diabetes; diabetes AND treatment; epilepsy; epilepsy AND treatment; lupus; depression; depression AND treatment.

To investigate pregnancy acquired risk factors, key words added included: multiple pregnancy; twins; triplets; quadruplets; higher order multiple pregnancies; planned pregnancy; unplanned pregnancy; short inter-pregnancy gap; long inter-pregnancy gap; gestational diabetes; diabetes in pregnancy; antenatal depression; antenatal depression AND treatment; pre-eclampsia; toxaemia; obstetric cholestasis; OC; antenatal day unit attendance; prelabour rupture of membranes; threatened preterm birth; preterm birth; gestation at birth; inpatient admissions; placenta praevia; low-lying placenta; abnormal placentation; placenta percreta; placenta accrete; placenta increta; antepartum h(a)emorrhage; APH; vaginal bleeding.

The same process was undertaken for intrapartum and labour and birth risk factors.

The literature reviewed in relation to data collection and electronic summary data were searched for on the same databases in addition the: European Clinical Research Infrastructures (ECRIN); US Food and Drug Administration (FDA); Data Protection Act; Principles AND Data Protection Act; NHS National Programme for Information Technology; Caldicott Guardian; Caldicott Guardianship; Principles AND Caldicott.

2.2.1 Definitions

2.2.1.1 Postpartum Haemorrhage (PPH)

The contemporary definition of PPH is still debated. Some favour the traditional definition of: "blood loss of 500 ml or more from the genital tract following childbirth". This definition was devised by a technical working group, with global representation, co-ordinated by the World Health Organisation more than 20 years ago (WHO, 1990a; WHO, 1990b). Whilst concurring with this volume for vaginal birth, the International Classification of Diseases (ICD 10-072) further defined haemorrhage following Caesarean birth as blood loss exceeding 750 ml (WHO, 2007a). Conversely, others state average blood loss at Caesarean section (CS) is 1000 ml (Pritchard et al., 1962; Stafford et al., 2008).

The American College of Obstetricians and Gynecologists (ACOG) have adopted this definition (ACOG, 2006), and subsequently it has been suggested that blood loss should only be classified as excessive, and termed "haemorrhage" when 1000 ml is exceeded following abdominal birth (Wise and Clark, 2008). The selection of this volume is justified by early seminal works which, by employing radiolabelled red blood cells (51Cr) to accurately measure blood loss, reported 7% of women bled 1000 ml following vaginal birth and 23% lost 1000-1500 ml following CS (Pritchard J.A., 1962). Using the same technique, Read and Anderton (1977) reported blood loss (mean +/-Standard Deviation) in primary CS as 1290 +/-240 ml and for repeat CS as 1012 +/-380 ml. However this study was small (n=30) and undertaken in elective CS. Therefore the impact of labour prior to CS on blood loss cannot be assessed.

Another proposed definition has been "excessive bleeding causing symptoms in the patient" However this is criticised because many women will have lost a significant amount (10-15% of their circulating blood volume) before becoming symptomatic (Devine, 2009). Another proposed, more objective, definition of PPH is a 10% decrease in haemoglobin or haematocrit levels from late pregnancy value. However the utility of this definition relies heavily on the time taken to obtain results if delay in diagnosis and treatment is to be avoided. Therefore the more clinical definition of "need for blood transfusion" has also been proposed (Combs et al, 1991). It could be argued, however, that any definition reliant on requirement for a specific treatment, might demonstrate evidence of provider practice, and resource availability, rather than the clinical condition of a patient.

Indeed, a review reported postpartum anaemia requiring transfusion occurred in less then 1% of vaginal births and 1-7% of CS, admitting that this range may be due to inconsistencies in definitions and thresholds for treatment (Jansen *et al*., 2005). Furthermore, transfusion guidelines have significantly changed in the twenty years since the definition was originally proposed.

General consensus in current practice is that PPH occurs at 500 ml, regardless of mode of delivery (NICE, 2007).

2.2.1.2 Classification of postpartum haemorrhage

Severe PPH is even less well defined, either using a blood loss volume (anything between 1000 ml and 2500 ml) or the need for blood products, and is dependent on resource availability (Brace and Penney, 2004; Knight, 2007; Carroli *et al.,* 2008). The Health Care Commission (2008) (now the Care Quality Commission) adopted different terminology defining "significant" PPH as ≥1000 ml and "major obstetric haemorrhage" as ≥2500 ml. The current RCOG Green-Top guideline classifies PPH as: minor when estimated blood loss is 500-1000 ml; moderate when estimated blood loss is between 1000 and 2000 ml; and severe, when estimated blood loss exceeds 2000 ml (Arulkumaran *et al.*, 2009).

Others advocate the number of units of blood required as definitive of massive haemorrhage. In Scotland, the definition of massive obstetric haemorrhage (MOH) is a blood loss volume of ≥2500 ml or a haemorrhage requiring ≥5 unit blood transfusion or treatment for a coagulopathy (Penney and Adamson, 2007a).

Elsewhere, 4, 6 and 10 unit transfusions fulfill the definition (Shevell and Malone, 2003; Macphail and Fitzgerald, 2001; Burke and Duignan, 1991).

Using blood loss volumes and blood product requirement to fulfill definitions whilst incorporating the slow blood loss attributable to surgery, does not encompass the rapidity of blood loss often seen in PPH, which requires urgent recognition and treatment. The rate of blood loss should be considered when assessing PPH, as this influences the woman's capacity to compensate, physiologically, for the blood loss (Macphail and Fitzgerald, 2001), and urgency of treatment response required. In a review document a working definition of the loss of 50% of blood volume in 3 hours was proposed, equating to a blood loss rate of 150 ml/min (Macphail and Fitzgerald, 2001). The WHO disagrees, evidence from a systematic review showed that exsanguination from undiagnosed or untreated postpartum haemorrhage, in a "well" woman, leads to death within 2 hours (Khan et al, 2006).

In real terms, the rate of 150 ml/min would result in a PPH of 1500- 2500 ml within 10-17 minutes in a woman of average weight (50- 70kg) with a circulating blood volume of approximately 5 litres, at term. Therefore, if associated morbidities are to be avoided, prompt recognition of the severity of the situation is essential when estimated blood loss reaches 1000-1500 ml, which could occur as soon as 6-7 minutes following birth.

There are inherent difficulties with all the "absolute" amounts fulfilling definitions of PPH, as each woman's response to a loss of a certain volume of blood may be different from that of another. The ability to "cope" physiologically following haemorrhage is determined by a woman's general health and nutritional status, and associations with lifestyle choices, socio-economic status and poverty are recognised (UNICEF, 2008; WHO, 2008; WHO, 2006a). Women with complex health and social issues are likely to be less able to tolerate and compensate for blood loss following birth (Lewis, 2007b).

The changes in nutritional status, lifestyle choices and demography of women giving birth today may mean that the seminal work, some undertaken more than 40 years ago, regarding blood loss and ability to compensate are different today (Pritchard *et al.,* 1962; WHO, 1990; Combs, 1991).

Furthermore, because circulating index blood volume ($_{IN}$BV), and total intravascular blood volume decrease in a non-linear manner in obese and morbidly obese people (Lemmens *et al.*, 2006), women with high body mass indexes (BMI) are potentially more vulnerable to blood loss, being compromised when losing lower blood volumes than their lean counterparts. Given the increasing number of women embarking on pregnancy with a high body mass index (BMI) (Heselhurst, 2010) this is especially important, and may necessitate further clarification of the definition of severe PPH. To date this has not been addressed in the literature, however, whilst not acknowledging associated comorbidities, or assigning causality, the latest CEMACH Report stated 50% of the women who died were overweight or obese (BMI >25Kg/m^2) (Lewis, 2007b).

2.2.2 The size of the problem

Globally, it is estimated more than 14 million women a year experience PPH at or shortly after giving birth (WHO, 2007b). This common obstetric complication causes more than 24% of all maternal deaths worldwide, equating to more than 132,000 women dying as a result of uncontrolled bleeding following childbirth (WHO, 2004). There is wide regional variation, but PPH is particularly problematic in parts of Asia and Africa, where it accounts for up to 30% of maternal deaths (Khan *et al.*, 2006). Deaths in low resource countries can be attributed, at least in part, to inherent complex social, infrastructural and health care issues. But even in Europe, every year, between 335 and 1000 women die during or shortly after giving birth. At the time of commencing this work, 13.2% of these maternal deaths were attributed to PPH according to a European survey aimed to describe mortality and morbidity across the member States (EUROPERISTAT, 2008). In the UK, whilst not the main cause of maternal death, 14 of the 132 (10.6%) women who died as a direct result of pregnancy in the last triennial report, were caused by PPH (Lewis 2007b). This equates to a mortality rate of 0.66/100,000 maternities.

In addition to PPH related mortality, it is estimated that more than 10 million women worldwide live with the short and long term consequences of PPH (UNICEF, 2004). As outlined in chapter 1, in the UK it is reported, using the UKOSS methodology, that for each woman who dies, 15 undergo peripartum hysterectomy (Knight, 2007). This equates to an incidence of 0.45 per 1000 births, comparable to the Netherlands (0.47 per 1000 births) (Kwee *et al.*, 2006), and lower than the rate reported in Canada (0.8 per 1000 births) (Glaze *et al.*, 2008) and parts of the USA (1.4 and 2.7 per 1000 births) (Kastner *et al.,* 2002; Bakshi and Meyer, 2000). The variation in incidence, before and after this current

work, is shown in Tables 1.1a and 1.1b. Most are calculated using retrospective case review, and differences may be attributable to practice variation with earlier resort to peripartum hysterectomy, or increased associated maternal morbidities including previous CS.

The impact of PPH on other morbidities (such as collapse, heart failure, intensive care admissions, prolongation of hospital stay, anaemia, blood transfusion, fatigue or mental ill health) is difficult to assess due to reporting inconsistencies, and the amalgamation of data for all severe morbidities. However an audit of intensive care admissions (ITU) suggested that of those women admitted during pregnancy or shortly afterwards, 72% were for haemorrhage (IRNARC, 2009). This figure must be viewed with caution because antepartum, intrapartum and postpartum bleeding are not differentiated, and this audit refers to females aged 16-50 years admitted to general ITU facilities. Women over 50 or under 16 years of age or treated in maternity high dependency units are not included.

2.2.3 Trends over time

In the UK, maternal death was relatively common at the start of the 20th century. Scientific breakthroughs, including the understanding of the integral role of oxytocin in uterine contractility (1906) and subsequent development of synthetic oxytocic's (Du Vingneaud *et al.*, 1953), made a significant impact on the maternal death rate. Alongside the discovery of antibiotics, improved surgical techniques, anaesthetic advances and the development of haematological sciences and blood banks, maternal deaths rapidly declined from 50/1000 maternities in 1900 to 8/1000 in 1950 (Chamberlain, 2006). However at the time of initiation of this research, in 2008, the total numbers of maternal deaths had remained remarkably constant throughout the previous 20 years (see Figure 2.1).

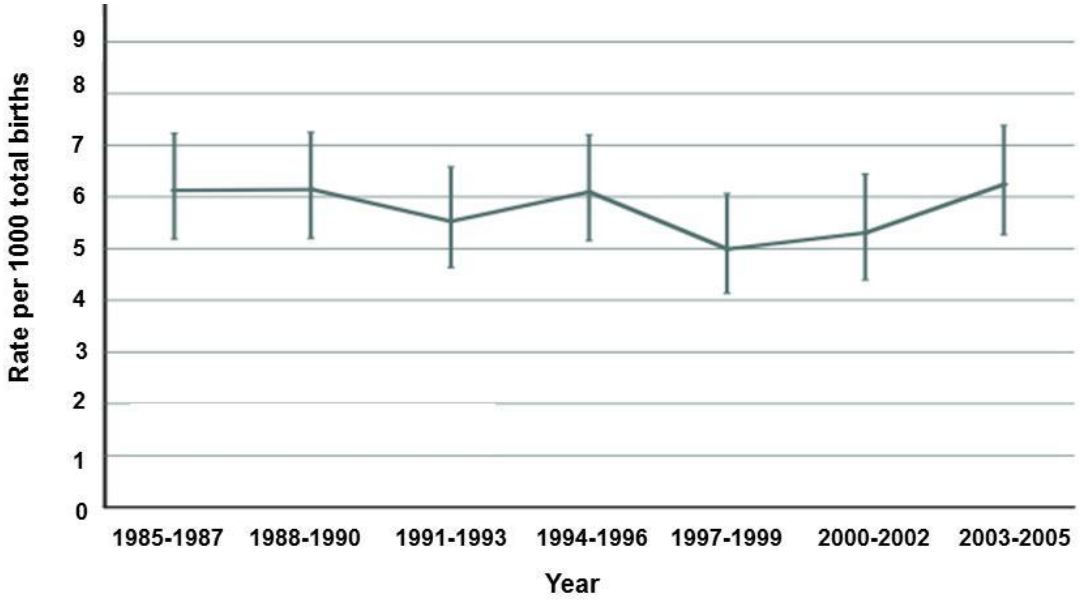


Figure 2.1: Maternal deaths (rate per 1000 births) in the UK between 1985-2005. (Lewis, 2007; p 5)

Line with error bars indicated direct death rates with 95% confidence intervals.

Chi Square =5.48, 6 df, p=0.48; Chi square for linear trend =0.48, p=0.49 (Lewis, 2007 b, page 5).

During this 20 year period a total of 130 women bled to death during childbirth despite improved surgical techniques, interventional radiology, arterial embolisation, novel drug development and autologous blood transfusion (Walfish *et al.*, 2009; Wise and Clark, 2008). Of these 130 deaths, 55 were simply attributed to PPH and the contribution of these deaths in each triennium is shown in Figure 2.2. Of the remaining haemorrhage related deaths, 27 were due to placental abruption, 22 caused by placenta praevia and 24 by genital tract trauma. The remaining 4 were attributed to uterine rupture.

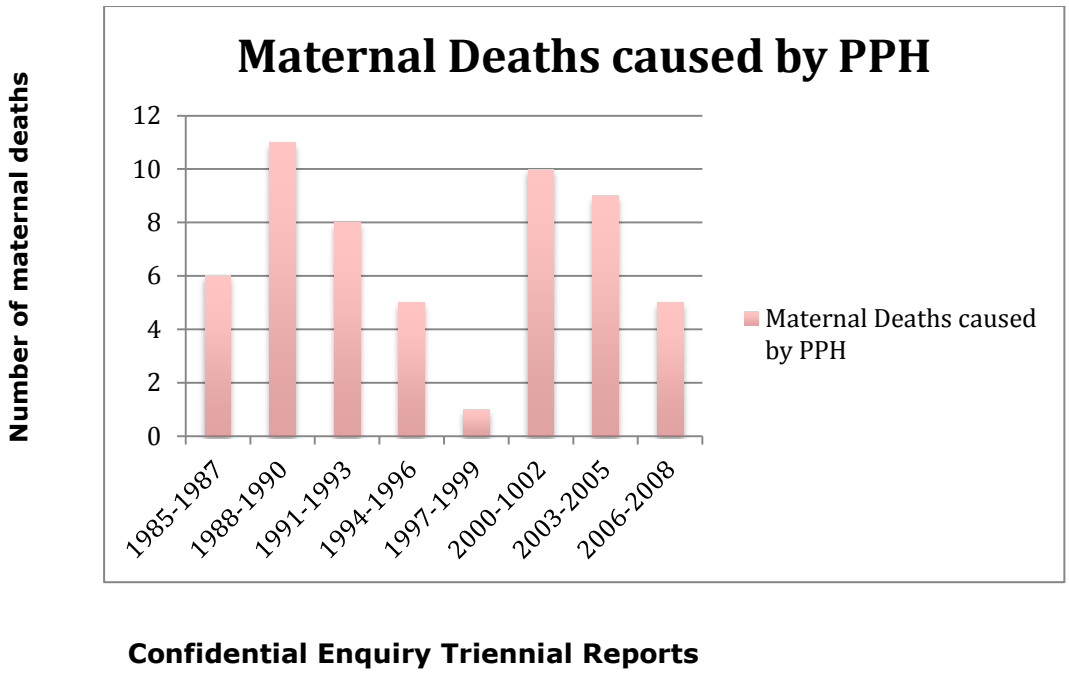


Figure 2.2: Contribution of PPH to UK maternal deaths 1985-2008 according to the Confidential Enquiry Reports (adapted from Fleming *et al*., 2012)

The first report into maternal deaths was produced by local governments in England and Wales in 1915, largely comprising of data from birth and death certificates to ascertain and investigate causes of death and geographical variations. During the intervening years, the system for recording and monitoring maternal deaths was developed, and the Confidential Enquiry into Maternal Deaths was introduced, in its current format, in the 1950s. PPH has been cited as a cause of death in every report as shown in Figure 2.2.

The incidence of PPH has always been difficult to assess reliably, with a consensus incidence of 1-10% generally reported in the literature (Carroli *et al.*, 2008; Henry *et al.*, 2005). This difficulty is attributed to variation in definitions and availability and quality of coded or raw data. Recent reports suggest a

temporal rise in the incidence of PPH in industrialised countries (Knight *et al*., 2009; Ford *et al.*, 2007a; Cameron *et al.*, 2006; Wen *et al.*, 2005). These retrospective studies relied on analyses of routinely collected clinical data, some of which was coded, and variable definitions, dependent on local practice, therefore the results should be considered with caution. Conversely, the incidence of PPH has been reported as low as 1-2%, with little associated morbidity, in 13 European countries; probably because this cluster randomised trial used a composite measure of severe PPH (one or more: blood transfusion, IV plasma expansion, arterial embolism, surgical procedure, ITU admission, treatment with recombinant factor VII or death), any of which are reserved only for the most severe cases (Zhang *et al.*, 2010). Despite this seemingly deflated PPH rate wide variation in incidence of PPH in participating countries was apparent (Winter *et al.*, 2007). Furthermore, in this work, data were collected from a single region in each country and this may further limit the generalisability of findings.

Others have sought to investigate the incidence globally, which has proved difficult due to absence of and variation in reporting mechanisms even in resource rich countries (Knight *et al.,* 2009). Heterogeneity of definition, practice variation, as well as reporting differences are cited as being likely contributors, concurring with earlier findings in Europe (Zhang *et al.*, 2005) and data from the WHO (Khan *et al*., 2006), Canada (Joseph *et al.*, 2007) and Australia (Roberts *et al.*, 2009).

An international collaboration that investigated trends in PPH in several high resource settings further concluded that PPH was increasing in Australia, Canada,

USA and the UK (Knight *et al.*, 2009). This increase was attributed solely to uterine atony in the USA, Canada and Australia. The rise in PPH was also directly associated with increasing rates of other serious adverse events in Australia, Canada, USA and the UK (Knight *et al.*, 2009). Knight and colleagues (2009), used routinely collected and categorised data in accordance with local definitions and classifications. Difficulties due to administrative differences in interpretation of International Classification of Disease Codes (ICD) and definition variability were reported. One country reported the proportion of women receiving a blood transfusion within 24 hours following birth as a surrogate indicator of PPH. Where ICD categorisation was not available, information was obtained from local sources, such as the United Kingdom Obstetric Surveillance System (UKOSS) survey of peripartum hysterectomy, and the Scottish Audit of Severe Maternal Morbidity. The majority of these systems rely on local reporting mechanisms and therefore potential omission of cases and questionable consistency and quality of information may limit any conclusions that can be drawn. For example, these data demonstrated an increase in PPH from 3.4 to 5.5 per 1000 deliveries between 2003 and 2007, but given the inconsistencies in definition and reporting and coding of PPH, in addition to changes in policies and practice during the study period, it is very difficult to ascertain the accuracy of this trend. Additionally these authors excluded "postnatal blood transfusion for low haemoglobin" from their analyses due to uncertainty that low Hb was caused by PPH. Therefore it is likely that PPH rates are under-reported in high resource countries.

A population-based study in New South Wales, Australia, using linked hospital discharge and birth records to assess incidence of PPH an increase from 4.7% to 6.0% between 1994 and 2002 was reported (Ford *et al.*, 2007a). In singleton pregnancies an increase was reported regardless of mode of birth. There was no

difference in PPH rates over time in multiple pregnancies, but this may be because the numbers of multiple pregnancies in this cohort was small. Ford and colleagues concluded that the increase was not attributable to the changing demography of childbearing women, although they reported increased numbers of women aged >35 years, immigrants, nulliparous women, placental abnormalities, post dates births and babies with birth weights ≥3500 g. Nor was the rise in PPH attributable to increased obstetric procedures, although there were increased numbers of CS, epidurals and induced labours. The authors identify variation and evolution of midwifery practice and components of active and expectant management of the third stage of labour over the course of the study. Unusually, in this study CS was reported as protective against PPH with both spontaneous vaginal and instrument vaginal birth conferring greater risk (Figure 2.3). (Ford *et al.*, 2007a). However this was probably due, at least in part, to the variation in management of third stage, which tends to be more diverse following vaginal birth and the adoption of higher rates of blood loss to define PPH following CS (>750 ml) in Australia.

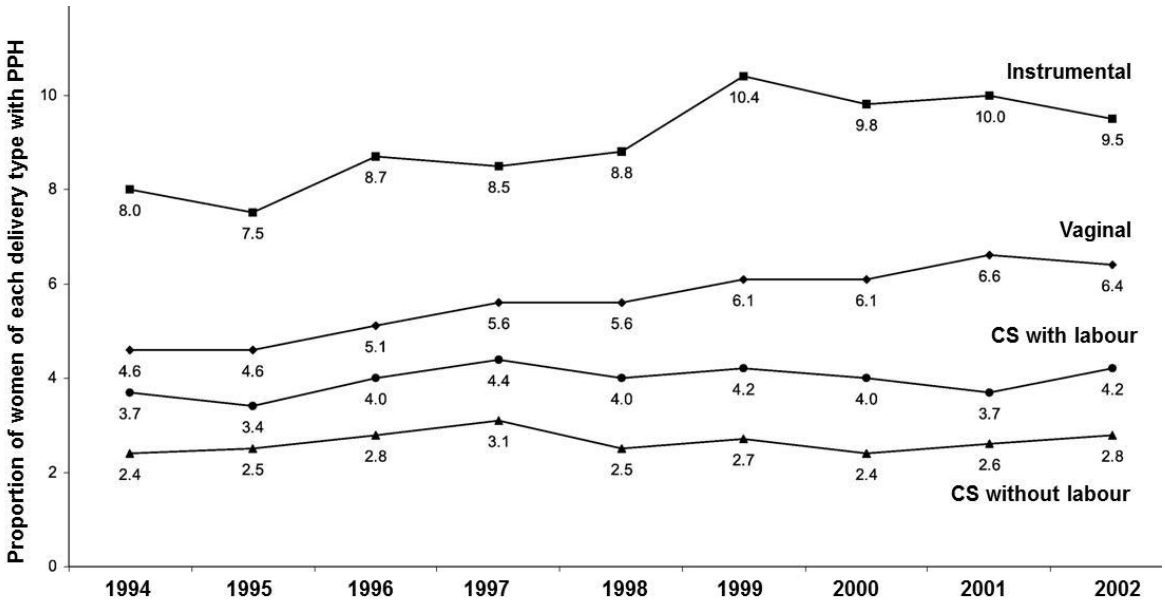


Figure 2.3: Incidence of postpartum haemorrhage (PPH) (defined as >500 ml following vaginal birth and >750 ml following Caesarean delivery) by mode of delivery for singleton pregnancies between 1994-2004 (taken from discharge summaries for women delivering in New South Wales, Australia) Instrumental and Vaginal Birth were both statistically significant. CS caesarean section. (Ford *et al*., 2007a: 240).

The Scottish Audit of Severe Maternal Morbidity (2010) using case review by local clinicians of data from 2008, acknowledged major obstetric haemorrhage (defined as ≥2500 ml or requiring ≥5 unit blood transfusion) as the most common cause of morbidity (4.3 per 1000 live births) and reported a halt in the upward trend seen in the preceding five consecutive audits (shown in Table 2.2, Lennox and Marr, 2010).

Table 2.2: Numbers and rates of women delivering in Scotland with major obstetric haemorrhage (defined as blood loss ≥2500 ml or requiring ≥ 5 unit blood transfusion), 2003-2008 (Lennox and Marr, 2010).

	2003	2004	2005	2006	2007	2008
Number of women (rate*)	174 (3.3)	163 (3.0)	233 (4.3)	271 (4.9)	256 (4.4)	257 (4.3)

*Women with major obstetric haemorrhage per 1000 live birth each year

Scotland is the only region of the UK to systematically collect data regarding maternal morbidity (Brace *et al.*, 2004). In all other areas limited data are available, primarily collected in accordance with Clinical Negligence Scheme for Trusts (CNST) requirements. Data are not circulated regionally or nationally and therefore comparisons cannot be made. The lack of routine and consistent data collection is surprising given that in countries where maternal death is rare, "near-miss" audit has long been advocated as a useful adjunct to mortality reports to examine adverse events and investigate substandard care (Mantel *et al.*, 1998; Mantel and Moodley, 2002; Pattinson *et al.*, 2003). Despite limitations of collection methods and reliance on local reporting and assessment of issues around severe adverse events most commonly by a risk midwife or manager in each health Board, and funding uncertainties for this system, the Scottish Severe Morbidity Audit has reported a year on year reduction in associated substandard care (Lennox and Marr, 2007).

2.2.4 Risk factors and causes

Causes of PPH have been identified in the literature for many years, with many striving to identify those most at risk and therefore provide the opportunity to predict and prevent these events. Traditionally the causes of PPH have been referred to as the "4 Ts": Tone, Tissue, Trauma, and Thrombin, which are summarised in Table 2.3.

Table 2.3: Summary of risk factors for PPH (adapted from Devine and Wright, 2009).

Pathophysiology	Underlying Causes	Clinical risk factors
TONE Abnormal uterine contractility	Over distended uterus	Multiple gestation, polyhydramnios & macrosomia.
	Uterine muscle fatigue	Prolonged or augmentation of labour & previous PPH
	Chorioamnionitis	Prolonged ROM Spontaneous preterm birth Cervical insufficiency
	Uterine distortion/ abnormality	Fibroids & placenta praevia
	Uterine-relaxing drugs	Beta mimetics, Magnesium Sulphate & anaesthetic drugs
TISSUE Retained products of conception	Placenta accreta Placenta percreta Placenta Increta	Manual removal of placenta & succenturiate lobe
TRAUMA Genital tract trauma	Lacerations to the: Cervix, vagina and/or perineum	Precipitous labour, macrosomia, shoulder dystocia, operative delivery & episiotomy (especially mediolateral)
	Extension/laceration at Caesarean section	Deep engagement, malposition & malpresentation
	Uterine rupture	Previous uterine surgery.
	Uterine inversion	Fundal placenta, grand multiparity, excessive traction on umbilical cord
THROMBIN Abnormalities of coagulation	Pre-existing clotting abnormalities: Haemophilia, von Willebrands & Hypofibrinogenaemia	History of coagulopathy or liver disease
	Acquired in pregnancy	Sepsis
	Disseminated intravascular coagulation (DIC)	Intrauterine fetal demise
	HELLP syndrome	Haemorrhage Pre-eclampsia
	Anticoagulation	

The impact of traditional and newly identified factors have been explored and current evidence is explored in this section.

2.2.4.1 Causes of increases in PPH

Using birth records and discharge data Ford and colleagues (2007) identified associations between the upward trend (1994 to 2002) with abnormal placentation, macrosomia, and oxytocin (Syntocinon®) use. But concluded that changes in practice during the study period were more likely to be causative of increased PPH rates. Specific changes highlighted were, increased use of physiological third stage, more choice for health care professionals regarding uterotonic agents, reduction in the clinical time midwives spent during training and decreasing number of practicing midwives. Again, variation of definitions and local coding inconsistencies make comparison and conclusions difficult. In addition, several previously identified risk factors were excluded from modeling due to small numbers reported, these included, anaemia, pyrexia in labour, amnionitis, high maternal weight gain. But potentially more importantly datapoints not available for the duration of the project were also excluded and these included: placenta accreta, previous CS and vaginal birth after CS (VBAC). Therefore it is possible that maternal characteristics may have more impact on rising PPH rates than reported by these authors.

Using coded data from an anonymised patient record census Cameron and colleagues (2006) attributed the increased rates of PPH, from 4.9% in 1994 to 6.3% in 2002, which after adjustment for under reporting increased from 8.3% to 10.7% over the same time frame, to differences in maternal characteristics

(notably maternal age and BMI), variations in obstetric practices (increased use of physiological third stage) and improved ascertainment and reporting of PPH (registry records) (Cameron *et al.*, 2006). Whilst these data represented a State wide population, and therefore truly represented women giving birth in the time frame, there were concerns regarding data quality within this dataset, particularly under-reporting, which was identified as up too 41% in key items, when a sample set of cases were reviewed in detail (Taylor *et al*., 2005).

Whilst improved ascertainment of cases is desirable, apportioning causality to maternal characteristics and variation in practice would appear to present opportunities to revert the trend, especially in resource rich countries. These authors used retrospective coded data, and without further details of clinical scenarios the implications may be difficult to interpret.

In contrast, Wen and colleagues (2005), using coded data, but with broader admission and treatment categories, compiled by the Canadian Institute for Health Information, identified increased numbers of women embarking on pregnancy with pre-existing conditions, repeat CS births, and changing transfusion policies as contributory to the upward trend in Canada (Wen *et al.*, 2005). In the UK, using the UKOSS reporting methodology Knight (2007) reported increased incidence of placenta accreta, increta and percreta, ruptured uterus and infection as contributory to incidence of peripartum hysterectomy to control bleeding (Knight, 2007). Yoong et al (2006), used retrospective case review to investigate peripartum hysterectomy over 20 years in a multi-ethnic UK population, reported maternal ethnicity as contributory, in addition to previous

and current CS, abnormal placentation and morbidly adherent placentas (Yoong *et al.*, 2006).

Thus the reasons for the increasing trend of PPH is likely to be multifactorial and may not be simply attributable to increased CS rates as might be anticipated (Cameron *et al.*, 2006; Ford *et al.*, 2007a; Brace *et al.*, 2007).

The clinical risk factors identified here are by no means inclusive.

2.2.4.3 Pre-existing or pre-pregnancy risk factors

A range of pre-existing or pre-pregnancy risk factors for PPH have been identified in the literature:

1) Maternal ethnicity, particularly Hispanic and Asian (Combs *et al.*, 1991) and non-White women, reported as "women of colour" (Guendelman *et al.*, 2006) have been noted as at increased risk of PPH. Although ethnicity is variably reported, and comparisons not uniform, therefore confounding the impact of ethnicity. Additionally immigration patterns have changed considerably since Combs early case control study, and Guendelman and colleagues used data from the California Office of State Health Planning and Development, and excluded the smallest minority ethnic groups. In common with other reports using similar data sources, it is not clear whether ethnicity is self reported or by what criteria it is assigned.

African American women were also described as at increased risk of pregnancy related death, because they have more existing co-morbidities, including lower

haemoglobin (Hb) concentrations prior to PPH (Harper *et al.*, 2007) and uterine leiomyomas (Laughlin *et al*., 2009, Wise *et al*., 2007). Also in USA, using national datasets Black women have been described as 5 times more likely to die than White women due to pregnancy associated conditions, with the exception of PPH (OR 0.80 [95%CI 0.5 to 1.0]). Even so, those Black women who did experience PPH were 3 times more likely to die (Tucker *et al.*, 2007). Using routinely collected State wide data to identify ethnic disparities in relation to specific outcomes, including PPH, in an area with universal health care provision, it has been suggested that all women in minority ethnic groups are at increased risk of adverse health outcomes due to discrimination and inability or reluctance to engage with services (Sundararajan *et al.*, 2007). A retrospective follow up study showed ethnic minority groups were also over represented in women requiring intensive care following childbirth (Keizer *et al.*, 2006). However Keizer and colleagues (2006) reported 18.3% (26/142) of all intensive care (ITU) admissions were for PPH, of whom 77% (20 women) were white. Although the impact of specific ethnicities could not be assessed, it could be suggested that massive PPH requiring ITU admission, unlike other morbidities, is less problematic in non-white women. Additionally women receiving high level care, but not admitted to general ITU, were excluded from this analysis, and there was no adjustment for changing admission criteria during the 12 year study period. Such adjustment and the inclusion of cases treated in Obstetric High Dependency Units might have altered these findings.

It could be argued that appropriately targeted preconceptual and antenatal care to reduce associated morbidity, for example, weight management, treatment of hypertension and routes of access to care, could, in part, ameliorate the impact of ethnicity. However these data should be considered cautiously as ethnicity is variably defined. Guendalman and colleagues (2006) compared broad categories

of Latina, non-Latina and Asian women; Harper and colleagues (2007) categorised women as African-Americans and White-Americans; whereas Tucker *et al*., (2007) simply used Black or White. Thus, no consideration was given to the areas in Africa or geographical differentiation between a Black or White person. Neither was duration of immigration considered. Sundararajan *et al.* (2007), whilst advocating areas of universal health provision as appropriate to assess the influence of epidemiological factors, acknowledged limitations in reporting ethnicity within their population. Combs *et al*. (1991) categorised ethnicity as Black, White, Hispanic, Asian or other and more recently, Keizer and colleagues (2006) used Caucasian, Surinam, Moroccan, Turkish, sub-Saharan African and Asian. Uniformity of definition, and categories used, would facilitate easier understanding of the impact of ethnicity on blood loss (Keizer *et a*l., 2006). When investigating risk factors associated with PPH >1000 ml following vaginal birth Asian ethnicity increased risk OR 1.8 (95%CI 1.4 to 2.2) (Magann *et al*., 2005). Using the same database this was not apparent in women delivering by emergency or elective CS, but this could be due to differences in the ethnicities and smaller numbers of women delivering abdominally (Magann *et al*., 2006).

2) Older maternal age has been identified as a risk factor for many adverse pregnancy outcomes in a review document using the National Swedish Dataset, which is renown for complete and accurate data (Montan, 2007). Although the association between maternal age and PPH has been variably reported with no increased risk reported in a cross sectional study (Roberts *et al.*, 1994) and increased risk of severe haemorrhage incrementally increasing with age ≥30 in data from the Norwegian National Register (Al-Zirqi *et al.*, 2008). The independent effect of age is difficult to ascertain as the higher incidence and impact of co-morbidities with older age is not always described or adjusted for (Al-Zirqi *et al.*, 2008; Montan, 2007). Roberts *et al.* (1994) concluded that PPH

was not influenced by maternal age, however this cross sectional cohort analysis was undertaken when the proportion of women giving birth aged ≥35 years was smaller than currently, and therefore these conclusions may be less relevant today. Uterine fibroids are also associated with increasing maternal age. One self report survey of Black women, with diagnoses confirmed by ultrasound or surgery evidence, reported highest incidence in women aged 40-45 years (Wise *et al*., 2005). Earlier work, also in the USA, reported a linear relationship with age and incidence of fibroids in Black and White women aged between 35 and 49 (Baird *et al*., 2003). This study population was randomly selected from a health insurance company, and therefore the influence of healthcare provision cannot be ignored.

Additionally these authors concluded that potential adverse events could easily be managed within the context of modern obstetric services, contradicting more recent reports of increasing maternal morbidities associated with medical interventions (Al-Zirqi *et al.*, 2008), but potentially contributing to rising CS rates seen in older women (Smith *et al.*, 2008).

Geller and colleagues (2004) reported the highest levels of mortality and morbidity in women aged between 20 and 34 years old, but this may be reflected by three times fewer women aged ≥35 years in all aspects of the mortality to morbidity continuum (Geller *et al.*, 2004). Whilst teenage pregnancies have been associated with some adverse pregnancy outcomes, there is no reported association with PPH (Al-Zirqi *et al.*, 2008). This may be attributable to more efficient uterine contractility, smoking habits or higher rates of spontaneous vaginal births (Lewis *et al.*, 2009).

3) Obesity, expressed as high BMI (≥30 kg/m^2), has been variably associated with PPH. A retrospective cohort study using data from the Aberdeen Maternity and Neonatal Databank where early pregnancy measurements of maternal height and weight calculated BMI, showed that although blood loss increased in a linear relationship with increasing BMI, PPH was statistically significant in obese women (Bhattacharya *et al.*, 2007). Conversely data from the Nova Scotia Atlee Perinatal Database reported no relationship between obesity and PPH, although these authors, rather than using BMI, defined obesity as a pre-pregnancy weight of ≥90 kg. Women weighing > 75 kg but <90 kg were excluded, as were women weighing <50 kg, and those weighing 50-75 kg were the referent range (Robinson *et al.*, 2005). Whilst women weighing > 90 Kg are likely to be obese, despite the limitations of BMI, the degree of obesity is not apparent and this limits the generalisability of these authors findings. If indeed, these women were morbidly obese, these findings would concur with those Bhattacharya.

In retrospective case review studies in different areas of the UK, obesity has also been linked with poor uterine contractility leading to increased rates of induction, augmentation and CS (Zhang *et al.*, 2007) and prolonged third stage of labour (Usha Kiran *et al.*, 2005). A further UK database reported that, conversely, being underweight (BMI<19 kg/m^2) was protective against PPH (Sebire *et al.*, 2007a), this was confirmed using a slightly different definition (BMI<20 kg/m^2) (Denison *et al.*, 2008). Many of the studies investigating the effects of obesity have relied on epidemiological or clinical databases (Bhattacharya *et al.*, 2007; Robinson *et al.*, 2005) and are, therefore, reliant on the accuracy of blood loss assessment and entered or coded data, with no recourse to medical records to confirm details. One such study, employing the highly regarded Swedish National Register, reported a linear increase in incidence of PPH with increasing BMI (Denison *et al.*, 2008) contradicting the findings of others, who have suggested that those at

greatest risk were the obese, but not the severely obese (Robinson *et al.*, 2005). However the definition of severe obesity in this latter cohort was 'weight exceeding 120 kg', making comparison difficult, as weight alone does not discriminate level of obesity. BMI, although widely utilised, has been identified as a crude measurement of obesity and indicator of health status (Cawley and Burkhauser, 2006). Despite these limitations the overall evidence suggests that obesity is linked to PPH, although with these data there is seldom any adjustment for confounding factors associated with obesity.

4) Social deprivation and poverty are complicated to measure, but poverty has been associated with maternal obesity, risky health behaviours, low educational attainment and lack of engagement with services, leading to adverse pregnancy outcomes (Nagahawaite and Goldenberg, 2008; Lalonde *et al*., 2006; Vais and Bewley, 2006). Waterstone *et al.,* (2001) employed a complex strategy to assign social exclusion. This included: social categories according to the UK Registrar General, extended to include information regarding marital situation and male partner's employment status; social exclusion was further considered to be present when notes review revealed one or more of: concealed pregnancy; age <16 years; poor housing; low income (on "income support" documented); previous child in local authority/state care (current or previously); in trouble with the law (currently or previously); living alone (partner abroad or "unsupported" documented in notes); unbooked; unwanted pregnancy; currently or previously in foster care; care order being considered for unborn child; social worker involvement or alcohol dependency. This would appear to be cumbersome and not necessarily generalisable or applicable as social norms evolve. Even so, their comprehensive case control study reported social exclusion, in accordance with this definition, reported OR 2.91 (95%CI 1.76 to 4.82) for severe PPH (1500 ml) (Waterstone *et al.,* 2001).

Others have suggested poor maternal nutrition, food insecurity, and associated psychosocial factors may be more contributory of adverse pregnancy outcomes. Certainly links between such socioeconomic indicators and preterm birth and perinatal infections have been identified in a prospective cohort study (Laraia *et al*., 2006), but the impact on PPH has not been assessed. Multi-level health care provision, dependent on ability to pay, influences women attending for care, further complicating comparison (Nagahawaite and Goldenberg, 2008; Costello *et al.*, 2004).

A universal health care system, as provided by the NHS, and other areas such as Victoria, Australia, should eliminate such differences. However the Health Survey for England 1998, 1999, 2000, showed systemic inequalities in healthcare use in relation to income, ethnicity, employment and low educational achievement (Morris *et al*., 2005). Higher formal educational attainment was associated with fewer GP and outpatient appointments and certain ethnicities attend for primary care but are not proportionally referred for specialist care (Morris *et al*., 2005). However these findings referred to general health and predated NHS reforms, therefore extrapolation to pregnancy may be inappropriate to maternity services, and also to postdating the reforms. Earlier work to develop a theoretical framework to assess inequities in health care in the UK also concluded these existed in some domains (Goddard and Smith, 2001). But similarly maternity services were not included. A qualitative study, nested in a larger survey, of Somali women who were refugees and asylum seekers reported communication as the major barrier preventing access to maternity care, compounded by specific health needs, namely the high prevalence of female genital mutilation (Harper Bulman and McCourt, 2002). A cross-sectional postal survey using a stratified clustered random sampling strategy concluded that women were more likely to book late for antenatal care if they were born outside the UK or non-cohabiting; there was no difference according to social economic classification or age at

completion of full time education (Rowe *et al*., 2008). It could be argued that completion of a postal questionnaire demands a level of education, and therefore these data may exclude a relevant group. Although an earlier systematic review investigating social and ethnic disparities in antenatal screening tests reported inconsistent uptake with different screening tests, with South Asian women least likely to receive prenatal screening this was potentially because fewer of these women were offered the tests (Rowe *et al*., 2004). As screening has become more universal, it could be hoped that this is no longer the case.

Others have suggested that social support determines health in mothers and babies, rather than class (Oakley *et al.*, 1994), which could concur with the finings of Rowe *et al*., (2008) regarding single women tending to delay initiation of antenatal care. Conversely, it would contradict associations between ethnicity and poor outcomes as many cultures form supportive communities.

A joint WHO/FIGO statement (2006) described PPH as an 'equal-opportunity incident' due to its unpredictability. This suggests that it is the existence and ability of health systems to deal with PPH that makes poorer people more likely to suffer associated morbidities (Lalonde *et al.*, 2006). This might be particularly applicable in countries with multi-level health care based on the ability to pay, but would appear less relevant in a universal system like the NHS.

5) Maternal smoking at first antenatal appointment has long been associated with preterm birth, intrauterine growth restriction, and fetal demise (Meyer and Tonascia, 1977), in addition to placental abruption and placenta praevia (Ananth *et al.*, 1996). Both these epidemiological studies used perinatal registers that

captured data regarding smoking at first antenatal contact. The information was self reported, the accuracy of which is variously described (Stevens and Munoz, 2004). Additionally there was no account of changing habits throughout pregnancy. The effects of smoking on uteroplacental blood supply are therefore controversial, both appearing to be inadequate, leading to reduced fetal growth but also associated with bleeding due to abnormal placentation and premature placental separation. In a case control study Waterstone and colleagues (2001) reported a protective effect of smoking at booking with subsequent severe PPH (≥ 1500 ml) OR o.65 995%CI 0.44 to 0.96). Maternal smoking has also been associated with lower antenatal haemoglobin concentrations (Bodnar *et al.*, 2004), which have also been associated with PPH (NICE, 2007). These data were obtained from a randomised control trial of iron supplementation in a low socioeconomic population, and adjustment for other confounders and compliance data were not included. There are no published data on the impact of paternal or household smoking and therefore the impact of passive smoking could not be assessed.

6) Primiparity and multiparity have been variably associated with risk of PPH (Sheiner *et al.*, 2005; Williams *et al.*, 1998). Primiparity was reportedly a major risk factor for massive PPH, defined as blood loss >1500 ml, in a UK study (Hazra *et al.*, 2004). However this study reported an incidence of 0.5%, investigating just 145 cases, and using retrospective computerised data to identify cases and clinically assessed blood loss volumes, the method of assessment was not clarified. Furthermore identification was achieved through electronic summary data no evidence of clarification for erroneous data. This may have influenced these findings, as potential under reported volumes in summary data were not investigated. The authors propose inappropriate management of women not traditionally considered at risk as the rationale for their finding. No report of

management of the third stage is included and it is therefore difficult to assess this conclusion. However, the identification of primiparity as a risk factor was not novel, although the earlier study investigated PPH >500 ml using retrospective coded records for a discreet geographical area (Hall *et al.*, 1985).

Grand multiparity has been historically associated with increased risk (Babinszki *et al.*, 1999), despite definition difference of ≥4 (Bibi *et al.*, 2007) or ≥5 (Humphrey, 2003) previous births after 20 weeks' gestation. However more recently several authors have reported grand multiparity as negatively associated with PPH (Hazra *et al.*, 2004; Mousa and Walkinshaw, 2001). These observational studies, both historical and more recent, whilst reporting on index pregnancy outcomes, commonly did not account for other confounding factors, such as previous obstetric history. Babinszki and colleagues (1991) reported all grand (n= 314) and great-grand (n= 133) multiparas were all aged over 35 years and therefore used this criterion to select the comparison group. Great-grand multiparity, defined as >9 previous births, whilst increasingly rare in high-income countries, was not associated with PPH (Babinski *et al.*, 1999). As the average family size has decreased in recent years, this may be a less important risk factor than previously considered (Glinianaia *et al.*, 2008) and active management strategies for these rare women may be contribute to the non-association with PPH.

Long inter-pregnancy spacing has also been proposed as increasing labour dystocia and incurring subsequent adverse effects, including PPH (Conde-Agudelo *et al*., 2007), contradicting the findings of earlier authors (Orji *et al.*, 2004). But these findings may be more relevant than previously, due to societal trends of serial monogamy. Others have reported short inter-pregnancy spacing

in women who delay initiation of childbearing (Nabukera *et al.*, 2009). This retrospective cohort study, using regional linked registration data, merely focused on pregnancy booking interval data and therefore the impact of short inter-pregnancy spacing on PPH (and other pregnancy outcomes) could not be assessed.

7) Assisted conception techniques result in around 12,000 UK births each year (http//:www.hfea.gov.uk) and birth registry data have shown they are associated with various pregnancy complications (Shevell *et al.*, 2005) including abnormal placentation (Romundstat *et al.*, 2006) and PPH (Breheny *et al.*, 2009). Although many of these studies are large, the majority of women conceived spontaneously and the numbers achieving pregnancy with specific assisted reproduction techniques (ART) were small. Therefore caution should be exercised when interpreting these results (Shevell *et al.*, 2005). Despite guidelines advocating single embryo transfer (RCOG, 2007), ARTs are also associated with increased numbers of multiple pregnancies, which are also associated with PPH, but this was not the explanation in the studies cited, as only singleton pregnancies were included (Romundstat *et al.*, 2006; Shevell *et al*., 2005).

Similarly women achieving pregnancy as a result of ART are more likely to be older than women conceiving spontaneously (Breheny *et al.*, 2009), but rarely is maternal age adjusted for when investigating the impact of these technologies. It has also been suggested that underlying reasons for infertility, for example endometriosis, or specific treatment regimens, such as in-vitro fertilization, may be causative of excessive bleeding following birth (Kallen, 2008). Further investigation may inform women and health service providers regarding place of birth, mode of delivery and third stage management.

8) Previous PPH has long been identified as a risk factor in subsequent pregnancies (Ford *et al.*, 2007b; Kominiarek and Kilpatrick, 2007; Newton *et al.*, 1961). However history often relies on maternal report, especially when previous maternity notes are unavailable. Inaccuracies in information are possible due to varying definitions and limited maternal understanding. Advances in technology facilitate the emergence of large regional and national databases with the potential to gather and link information, as achieved by some authors, but reporting consistency needs to be assured. Earlier work, undertaken in smaller networks, without computerised systems, although more labour intensive, may have provided more accurate data (Doran *et al.,* 1955).

One of the earliest studies investigating repeated PPH using data State University of Iowa Hospitals from 1936-1945 with a PPH definition of blood loss exceeding 600 ml, reported a PPH rate of 5.2% following spontaneous vaginal birth, but the recurrence rate was 8.1% Doran *et al.*, (1955). Of these 68% (21/31) were attributed to the same cause as the initial haemorrhage. This suggests recurring risk factors may be contributory. However these authors excluded caesarean births (1.7% of all deliveries) and counted multiple births as one, which may have influenced their findings. However, Dewhurst and colleagues (1957) reported a 23% recurrence rate, which increased to 28% with ≥2 previous PPH. This study, however, was considerably smaller involving 132 women. In 1991 Comb and colleagues reported previous PPH had OR of 3.55 (95%CI 1.24 to 10.19) for recurrence (defined as a fall in haematocrit by 10 or more points from pre delivery result or blood transfusion). These authors constructed a logistic regression model and previous PPH was one of the strongest predictors of the 17 factors included (Combs *et al*., 1991). Similar findings were reported in a single centre review of 19,476 births. Defining PPH as >1000 ml or need for blood transfusion, the PPH rate following vaginal delivery was 5.15%, and prior PPH had

an OR of 2.2 (95%CI 1.7-2.9) (Magann *et al*., 2005). In the UK a case control study investigating severe maternal morbidities, defining PPH as, estimated blood loss exceeding 1500 ml or fall in haemoglobin concentration of ≥40 g/l or ≥ 4 unit transfusion, previous PPH was associated with OR 2.74 (95%CI 1.69 to 4.44) (Waterstone *et al*., 2001).

The risk of recurrence in women who required bilateral hypogastric artery ligation to arrest bleeding in a previous pregnancy has been reported in a small case review study, of 13 pregnancies. Three women had PPH; 2 following vaginal births and reported as "easily managed…" and another successfully treated with prostaglandins at caesarean birth. This is the largest reported follow up study of pregnancies following hypogastric artery ligation, and despite the limitations of small numbers the recurrence rate of 27% is significant (Nizard *et al*., 2003).

Recurrence of PPH in women with previous uterine artery embolization to treat PPH has been investigated in a cohort study (n=28), of the 4 women who subsequently gave birth, all experienced PPH, 2 of whom required hysterectomy (Salomon *et al*., 2003).

Case reports of outcomes of subsequent pregnancies following B-Lynch and other compression sutures alone or in combination with other treatments are few and therefore it is difficult to interpret the impact of these on recurrence of PPH (B-Lynch *et al*., 1997; Api *et al*., 2005).

Retained placenta and associated PPH has been identified as recurrent events. A Norwegian collaboration identified women with retained placenta from medical

records of 24,750 births over 5 years. Retained placentas, requiring manual removal, occurred in 0.66% of cases (n=165) and 10% of these had a PPH; although blood volume is not described, but PPH attributed to decrease in pre and post delivery haemaglobin. Seventy-four of the 165 women with retained placenta were parous and of these, 12 (16%) had a retained placenta in their previous pregnancy (Tandberg *et al*., 1999). The overall incidence of retained placenta in this study is low, although the authors used multiple data sources to identify women requiring manual removal of placenta. Even so, previous retained placenta was similarly identified as a risk factor in subsequent pregnancies in a case control study of 113 women with retained placenta, logistic regression analysis showed OR 9.8 (95%CI 1.1 to 85.5) (Titiz *et al*., 2001). The wide confidence intervals seen in this study is due to the small sample size and therefore means the results should be viewed with caution. Furthermore a large Australian study identified prior retained placenta as a risk factor for PPH >1000ml and >1500 ml at subsequent non-elective CS (Magann *et al*., 2006).

Uterine inversion is associated with PPH, but is a rare event, estimated to occur in 1: 2500 births (Kominiarek and Kilpatrick, 2007). PPH reportedly occurs in 94% of cases (Platt and Druzin, 1981). An early study suggested uterine inversion occurred in 33% of subsequent deliveries, however a more recent case review of 40 cases where 65% has associated PPH and 47.5% required blood transfusion, found no recurrence in 26 subsequent pregnancies (Baskett, 2002). This case series took more than 24 years to complete, and therefore changes in practices and policies during this time may have influenced the results.

The impact of previous PPH can be difficult to assess as guidelines dictate women with a history of PPH are actively managed in the third stage of subsequent labours (NICE, 2007; RCOG, 2009).

9) Previous CS has been associated with subsequent adverse pregnancy outcomes, including repeat CS and abnormal placentation leading to excessive bleeding and associated morbidities (Magann *et al.*, 2006; Kwee *et al.*, 2006). In a prospective cohort study the incidence of placenta praevia has been reported as 5 times higher in women with a scarred uterus than multiparous women without a uterine scar (Chattopadhyay *et al.*, 1993). Furthermore, placenta praevia was complicated by accreta in 10% of cases with one previous CS and 59.2% after two or more abdominal births. In this study 4.5% of women embarking on pregnancy had previously delivered by CS. With increasing numbers of primary CS in the intervening years (Jarman, 2004) it is likely many more women embark on pregnancy following CS, and therefore these findings may be even more relevant. It is possible that women requesting CS may not consider the impact of this decision on subsequent fertility and pregnancy outcomes (Postnote, 2002).

A population based study in Australia of over 136,000 women showed that when compared with those having a previous vaginal birth, those previously delivered by CS and planned a vaginal birth subsequently had an OR 1.6 (95%CI 1.4 to 1.7; $p<0.0001$) for PPH, but were also at increased risk of uterine rupture in labour, peripartum hysterectomy and manual removal of placenta: all of which are associated with increased blood loss. Amongst those who were delivered by elective CS subsequently the risk of PPH was lower (OR 0.6 [95%CI 0.5 to 0.7]; $p<0.0001$) (Taylor *et al*., 2005). This study used Health Department and Births, Deaths and Marriages Registry data regarding first and second singleton births in New South Wales, Australia 1994-2002. This excluded multiple pregnancies and higher multiparous women, which may have influenced the results, as both have been associated with higher rates of PPH.

Ascertainment of the effect of previous CS on PPH could provide valuable information regarding risk of excessive blood loss in the future, with inherent value for women and health care providers.

10) Associations with maternal medical history and pre-existing medical conditions and PPH are variably reported. Given the variation in incidence of pre-existing diseases in the population, different risk profiles are inferred.

Epilepsy is variably reported as 0.2-0.4% and 0.7% of the antenatal population (Tomson and Hiilesmaa, 2007). Sonneveld and Correy (1990) reported increased rates of PPH in women who suffered epilepsy. However, no consideration was given to the drug regimes employed to prevent or minimize seizures, and issues of compliance were not addressed. Others report non-compliance with drug therapies as common, due to fears of teratogenicity, which Registry data show are largely dose dependent and less common with the new generations of medication available (Tomson and Hillesmaa, 2007). A case control study reported antiepileptic medication at antenatal booking being associated with several severe maternal morbidities, however the confidence intervals in all cases were wide, for example for severe PPH OR 5.75 (95%CI 1.20 to 25.72) (Waterstone *et al*., 2001). Therefore caution should be used in applying these findings, but the consistent increased OR may be indicative of clinical significance and therefore relevant to health care providers.

With anti-seizure medications increasingly prescribed for other psychiatric and neuropathic pain disorders, further investigation of associations with specific medications and management of pregnancies complicated by epilepsy is required.

The incidence of diabetes is increasing worldwide and the age at onset decreasing (Boyle *et al.*, 2001). Combined with the trend for women to delay motherhood,

many more women are at risk of pregnancy complicated by diabetes (Shand *et al.*, 2008). Whilst acknowledging the impact particularly of pre-existing diabetes on maternal and perinatal morbidity Shand and colleagues (2008) in their cross-sectional study using linked databases in Australia, reported no significant association with PPH or severe PPH (Shand *et al.*, 2008), concurring with earlier findings (Doran *et al.*, 1955), although this case review study used a different definition of PPH (≥ 600 ml as opposed to ≥ 500 ml). Similarly Waterstone and colleagues in a south of England case control study reported non-significant association with diabetes and PPH >1500 ml (Waterstone *et al*., 2001). Conversely in a small (n=182) regional database review it has been suggest that Type 2 diabetes is associated with a six times increased risk of PPH (Dunne *et al.*, 2003; Dunne, 2005;). Shand and colleagues (2008) used validated datasets and case notes to confirm diagnoses of both Type 1 and Type 2 diabetes. Using similar methodology, Dunne and colleagues (2003) investigated outcomes for women with Type 2 diabetes. This may contribute to the difference in findings.

A retrospective case control study investigating women with and without pre-gestational diabetes showed that women with either Type 1 or Type 2 diabetes were twice as likely to have PPH > 1000 ml than non-diabetic women (12% versus 6%) and estimated blood loss was also higher in the effected group (781+/-27 ml versus 642+/-0.2 ml) (Takoudes *et al*., 2004). In another Register study the Canadian Perinatal Surveillance System reported pre-existing diabetes mellitus complicated 1.29 per 1000 births and 2 of the 13 women who died with a pre-existing condition had diabetes (Wen *et al*., 2005). It is estimated that of those pregnancies complicated by diabetes 7.5% are Type 1 and 5% are Type 2 (NICE, 2008b). Given projected rates of diabetes for the coming years, the impact of diabetes demands extensive evaluation.

Inherited bleeding disorders, such as Von Willebrand Disease and haemophilia are known to be associated with PPH (James, 2006; Lee *et al.*, 2006). The incidence of Von Willebrand disease is reported as 1.3% (James, 2006). Most of the evidence regarding von Willebrand disease and association with PPH are case reports of less than 100 women and report incidences of 12.5% (Ramsahoye *et al.*, 1995) to 80% (Chediak *et al*., 1986) in 24 and 6 women restively. In a rare case control study of 102 women with von Willebrand's disease and 88 controls, 59% of women with the disease compared with 21% of the controls experienced PPH (Kirtava *et al*., 2003). The controls in this study were identified by the cases and PPH is described as "excessive blood loss". The high rate of PPH in this control group is curious and may be due, in part, to self report through telephone interviews and questionnaires.

Whilst haemophilia is sex linked, affecting males, female carriers have a 50% incidence of passing the defect to their sons, and the reported incidence of primary PPH in these women is 16% (24% for secondary PPH) (Lee *et al*., 2006). Guidelines exist for antenatal, intrapartum and postnatal care for these women, with unanimous agreement that women with such conditions should receive active management of the third stage of labour (Arulkumaran *et al.*, 2009; NICE, 2007: Lee *et al.*, 2006).

Women with connective tissue disorders are more at risk of PPH than the general population (Kominiarek and Kilpatrick, 2007), although the incidence varies according to disease, for example PPH in women with Ehlers-Danlos syndrome is 19% (Volkov *et al*., 2007), Gaucher 21-77% (Rosnes *et al*., 1996), Oesteogenesis Imperfecta 11% (Young and Gorstein, 1968), and Marfans syndrome 8-21% Rahman *et al*., 2004). All these conditions are relatively rare and therefore there

is a paucity of evidence around cases, suffice that health care professionals remain vigilant when managing labour and delivery in these women.

Until recently there was a paucity of evidence regarding the impact of female genital mutilation (FGM) on obstetric outcomes. A WHO study recently addressed this, and identified several adverse pregnancy outcomes, including PPH were increased in women who had experienced FGM (WHO, 2006; Johansen and Bathija, 2008). With the more extensive procedures conferring the greatest risk (Banks *et al.*, 2006). Whilst this large prospective observational study rigorously assessed the impact of FGM, the practice of antenatal defibulation in the UK, may lessen the impact of these procedures on PPH and other obstetric outcomes. Midwives working in multi-ethnic communities should be aware of the population at risk (RCN, 2006).

Uterine fibroids are likely to increase in size in pregnancy and are associated with increased risk of PPH (Jolley, 2009). One cross sectional study reported PPH in 10.3% of women with fibroids, but this study also reported high rates of dysfunctional labour and malpresentations, with no adjustments made for these potential confounding variables (Noor *et al.*, 2009). Additionally this study was undertaken in Pakistan and therefore transferability to a UK population may be limited. Using a large obstetric database with extensive information regarding 18,705 women giving birth between 1998 and 2002, and defining PPH >1000 ml and >1500 ml, Magann and colleagues identified fibroids as a cause of PPH (Magann *et al*., 2006), they reported OR 3.53 (95%CI 0.92 to 10.64) for blood loss >1000 ml, and OR 11 (95%CI 3.01 to 40.0) for blood loss exceeding 1500 ml. Despite not being statistically significant for >1000 ml, and with wide confidence intervals for >1500 ml, these OR are likely to be clinically significant

(Coggan, 2003). These authors proposed the distortion of the normal uterine architecture by leiomyomata preventing contraction of the uterine musculature as the rationale for PPH at both elective and emergency CS (Magann *et al*., 2006).

The odds ratio (OR) for PPH in women with asthma has been reported as 1.38 (95%CI 1.21 to 1.57) (Tata *et al.*, 2007). Using a well validated, primary care database these authors adjusted for maternal age, BMI and smoking status, and compared women with asthma with the general population. Severity of asthma was identified via codes for asthma diagnosis, medication prescriptions and exacerbation during the year preceding pregnancy. Unlike many complications, PPH was reportedly more common in women with mild asthma and no exacerbations, rather than more severe disease (Tata *et al*., 2007). Given the reported increase in incidence of asthma in women of childbearing age (3-8%) the association with certain obstetric complications, including PPH, needs further investigation in a contemporaneous population. Examination and comparison of treatment regimes may also prove valuable to ensure women receive optimal treatment for asthma, whilst reducing the risk of obstetric complications, including PPH.

2.2.4.4 Current pregnancy acquired risk factors

1) Multiple pregnancies have long been associated with many pregnancy complications, including excessive blood loss following birth (Sebire *et al.*, 2001b; Waterstone *et al.*, 2001), and attributed to the larger placental site, exaggerated maternal physiological responses to pregnancy and increased uterine stretch to accommodate more than one baby (Walker *et al.*, 2004). Magann and colleagues

(2005) investigating risk factors for PPH >1000 ml and/or need for transfusion following vaginal birth, reported OR 2.2 (95%CI 1.5 to 3.2) for multiple pregnancy. This was further increased to OR 5.1 (95%CI 1.5 to 15.7) when multiple pregnancy was complicated by twin to twin transfusion syndrome, although these were rare (0.8% of study population) so caution should be exercised interpreting this result. Increased incidence of multiple pregnancies has been attributed to increasing maternal age and ARTs (Practice Committee, 2004; Eriksson and Fellman, 2007), both have increased in recent years, and therefore are potentially responsible, at least in part, for the temporal rise in PPH.

2) Pre-eclampsia has been well documented as associated with abnormal bleeding, both placental abruption and PPH (Combs *et al.*, 1991). This could be due both to the endothelial dysfunction responsible for the atherosclerosis apparent in placental vessels, and the failure of spiral artery adaptation in pregnancy, which cause problems with placental adherence and vascular constriction following delivery of the placenta (Roberts and Cooper, 2001).
Furthermore the haematological disruption (haemolysis, elevated liver enzymes and low platelets) associated with pre-eclampsia may be contributory to the increased rates of PPH (Young *et al*., 2010), and clarifies the importance of differentiating between pre-eclampsia and gestational hypertension. Miller and colleagues (2007) reported an odds ratio of 1.49 (95%CI 0.99 to 2.23; p=0.05) for PPH in women with pre-eclampsia or gestational hypertension. Failure to differentiate between gestational hypertension and pre-eclampsia, the inclusion of vaginal deliveries alone and the additional impact of pregnancy at high altitude (Tibet, >3100 m above sea level) may limit the generalisability of their findings (Miller *et al.*, 2007).

3) Obstetric cholestasis (OC), whilst relatively rare (affecting <1% of the antenatal population), has been associated with adverse fetal outcomes and PPH (RCOG, 2006). The aetiology of abnormal liver enzymes and pruritus in OC remains uncertain, and the association with PPH equally unclear. One case control study reported PPH rates of 14.9% versus 1.38% in women with and without OC (Kenyon *et al*., 2002). In this study controls were selected as the next delivered woman, matched for age, ethnicity and parity, but given the definition for PPH used (>500 ml), the incidence appears very low in this arm, and inclusion of matching for mode of delivery may have been more appropriate, given the increased number of women with OC requiring emergency CS (14 versus 8). It is unclear as to whether prophylactic vitamin K was administered to women with OC despite PPH being identified as particularly problematic when this is not given. Mechanistically it is not entirely clear how vitamin K reduces PPH rates in women with OC (Kenyon *et al.*, 2002).

4) Placenta praevia, particularly major and anterior, is known to increase blood loss following delivery (Chattopadhyay *et al.*, 1993). A large database study investigating PPH associated with elective and emergency CS, reported the OR for EBL > 1000 ml (and/or transfusion) with placenta praevia as 6.65 (95%CI 3.24 to 13.09) and for > 1500 ml (and/or transfusion) OR 8.06 (95%CI 2.98 to 21.81) (Magann *et al*., 2006).

Factors associated with increased risk of placenta praevia include smoking (Ananth *et al.*, 1996), older maternal age (Montan, 2007) and previous CS (Coulter-Smith *et al.*, 1996). Therefore the impact of the changing demography of childbirth on the occurrence of placenta praevia and resultant PPH requires investigation.

5) Morbidly adherent placenta is a major risk factor for severe PPH and has been identified as commonly, but not exclusively, associated with placenta praevia (Chattopahdyay *et al.*, 1993). In this study, accreta was diagnosed according to difficulty in delivering the placenta, resulting in piecemeal delivery. It could be argued that this is moderated by operator competence (Chattopahdyay *et al.*, 1993). A more recent review, investigating the impact of abnormal placentation, reported an absence of randomised controlled trials, and therefore the level of available evidence remains limited (Oyelese and Smullian, 2006). Given the increasing incidence of placenta accreta, increta and percreta due to other demographic and pregnancy management changes, attending clinicians are advised to identify those at risk due to a previous history of uterine surgery. Indeed it has been suggested that morbidly adherent placentas are the "unintended consequences" of rising CS rates (Scott, 2008).

6) Other antenatal complications, events and illnesses associated with PPH include; antepartum haemorrhage (Bibi *et al.*, 2007), PPH > 1000 ml OR 2.92 (95%CI 1.90 to 4.45) PPH > 1500 ml 3.64 (95%CI 2.00 to 6.60) (Magann *et al*., 2006), antenatal anaemia, although haemoglobin levels of concern are variably reported (Kavle *et al.*, 2008; Singh *et al.*, 1998), antenatal blood transfusion PPH >1000 ml OR 4.80 (95%CI 1.02 to 20.67), > 1500 ml OR 9.01 (95%CI 1.94 to 41.94) (Magann *et al*., 2006) and acute fatty liver of pregnancy (Bonnar, 2000). A tenuous link with urinary tract infection may be due to other factors, such as maternal obesity, rather than a direct association (Usha Kiran *et al.*, 2005).

2.2.4.5 Intrapartum acquired risk factors

1) Gestation at onset of labour has been variably reported as influencing blood loss following birth. Preterm birth has been associated with PPH, potentially due to infection (Shennan *et al.*, 2006). However blood loss was a secondary outcome in this study. Preterm birth, <37 completed weeks of pregnancy, resulting in either elective or emergency CS has been reported as increasing risk of PPH >1000 ml and >1500 ml (OR 2.23 [95%CI 1.27 to 2.82] and OR 2.79[95%CI1.22 to 6.37] respectively) (Magann *et al*., 2006). Administration of corticosteroids, for fetal lung maturation, whilst undoubtedly beneficial for the neonate, confers no maternal benefit (RCOG, 2004), and has been associated with increased rates of PPH (Pattanittum *et al*., 2008). However these authors concluded that women receiving antenatal corticosteroids were more likely to have labour induced, and was twice as likely to have a CS. It could therefore be suggested that these cases were managed more actively, and other factors could contribute to PPH. Seminal work suggested that singleton, vaginal, preterm birth was significantly associated with prolonged third stage and retained placenta, which led to PPH (Combs and Laros, 1991). The relevance of this work is questionable, as prophylactic oxytocin was rarely used, and although some clinicians used controlled cord traction, others used techniques not currently in practice, such as the Credo manoeuvre and fundal pressure to expel the placenta (Combs and Laros, 1991). Prolonged gestation has been variably associated with PPH rates. It is difficult to determine the independent influence of gestation, as this is often associated with other factors, such as older maternal age (Zhang *et al.*, 2005), obesity (Sebire *et al.*, 2001c) baby birth weight (Sosa *et al*., 2009) and medical interventions, such as induction of labour (Stones *et al.*, 1993).

2) Fetal macrosomia has been associated with PPH (Gregory *et al.*, 1998), although the impact is difficult to assess due to its association with other factors, such as maternal obesity (Jolly *et al.*, 2003; Sebire *et al.*, 2001c) and both pre-existing and gestational diabetes (Mathew *et al.*, 2005). Conversely, Siggelkow and colleagues (2008) reported a direct correlation between birth weight and mode of delivery, but no increase in perineal trauma or PPH with infants weighing more than or less than 4000 g (Siggelkow *et al.*, 2008). This study involved 215 women whose infants weighed >4000 g, focusing on the influence of maternal gestational weight gain. These findings may be due to intrapartum management and other issues in this relatively small heterogeneous cohort. In a single centre observational study Hazra and colleagues (2004) reported no association with birth weight and severe PPH (defined as blood loss ≥1500 ml). However this study was relatively small, with 145 babies of which 26 (17.9% weighed more than 4 kg (Hazra *et al.*, 2004). Conversely a large population based cohort investigating risk of PPH associated with elective and emergency CS showed an OR 2.45 (95%CI 1.60 to 3.71) for PPH >1000 ml and OR 2.26 (95%CI 1.16 to 4.41) for PPH >1500 ml (Magann *et al*., 2006)

3) Induction and augmentation of labour are both associated with greater estimated blood loss using several methodologies including case control (Sheiner *et al.*, 2005) and retrospective database review (Duff and Sinclair, 2000; Hall *et al.*, 1985). Despite various investigations of induction techniques, (e.g. oxytocin versus misoprostol and dinoprostane) and mode of administration (orally, per vagina or intravenously) none has proved more effective at limiting primary blood loss (NICE, 2008a; Calder *et al.*, 2008; Bugg *et al.*, 2006; Majoko *et al.*, 2002; Hofmeyr, 2001; Stones *et al.*, 1993). Duration of oxytocin administration has not been investigated, but augmentation in the first or second stages of labour has been associated with both increased blood loss (Bugg *et al.*, 2006) and as having

no impact on blood loss (Hinshaw *et al.*, 2008). Conversely in a retrospective cohort study others report less postpartum blood loss following induction with prostaglandins, except where oxytocin is also required, unless this is continued until after the birth of the baby (Philip *et al.*, 2004). This suggests that oxytocin in the first and second stages of labour may lead to excessive blood loss in the third stage. Mechanistically, this could be due to the down regulation of myometrial oxytocin receptors in the presence of pharmacological concentrations infused during induction/augmentation (Phaneuf *et al.*, 2000). Combined with the myometrial lactic acidosis that occurs in dysfunctional labour, this leads to failure of the uterine contractility required to ameliorate bleeding after placental separation (Quenby *et al.*, 2004).

Other studies such as Magann and colleagues, do not whilst reporting labour dystocia as a risk factor for PPH > 1000 ml, but not > 1500 ml following emergency CS, do not give details regarding the methods of augmentation adopted (Magann *et al*., 2006). In an earlier investigation using the same extensive obstetric database these authors reported induction of labour resulting in vaginal birth as having OR1.5 (95%CI 1.2 to 1.7) (Magann *et al*., 2005). Prolonged first stage (defined as: latent phase exceeding 20 h for nulliparous and > 14 h in multiparous women; active phase < 1.2 cm per hour in nulliparous and <1.4 cm per hour in multiparous women) OR 1.6 (95%CI 1 to 1.6), and prolonged second stage of labour (defined as: > 2h with epidural; analgesia; >3 h without epidural) OR 1.6 (95%CI 1.1 to 2.1).

4) Duration of labour has been shown to influence blood loss. Precipitate labour, although variably defined (Thevakumar *et al.*, 2008), has long been associated with PPH (Brincat *et al.*, 1984). Similarly, the association of PPH with prolonged first and second stages of labour are well known (Magann *et al*., 2006; Hayash, 1990; Gilbert *et al.*, 1987). A literature review suggested that second stage of

labour duration ≥4 hours, whilst potentially associated with PPH, conferred no detriment for the infant but disempowers women (Williams, 2007). Little of the literature reviewed used electronic fetal monitoring and heterogeneity of the studies used compounded findings. Once labour is prolonged, prompt or delayed oxytocin administration has been shown to have no effect on blood loss (Hinshaw *et al.*, 2008). Reasons for dystocia and resultant slow progress are manifold, including advanced maternal age (Montan, 2007), obesity (Sebire *et al.*, 2001c), fetal macrosomia (Jolly *et al.*, 2003), fetal malpresentation or malposition (Chapman, 2004), ineffective uterine activity (Zhang *et al.*, 2007) and epidural analgesia (Roberts *et al.*, 2004). Prolonged third stage of labour has also been associated with increased blood loss (Bias *et al.*, 2004) and reasons cited for elongated third stage include maternal age ≥35 years, prolonged second stage of labour (>2 hours) (Magann *et al.*, 2008) and retained placenta (Combs and Lakros, 1991).

In a Dutch regional study using an obstetric database third stage of labour exceeding 30 minutes was identified as a risk factor for PPH (Bias *et al*., 2004). Magann and colleagues investigated the optimal time to remove retained placentas to prevent PPH in a randomised controlled trial which was not completed because 99.5% of placentas were delivered within 20 minutes (89% less than 10 minutes post birth) and therefore the sample size required to answer this question was unattainable (Magann *et al*., 2006b). A previous prospective observational study by the same authors had identified increased risk of PPH when delivery of the placenta did not occur within 10 minutes (OR 2.1[95%CI 1.6 to 2.6]), risk of PPH increased further at 20 minutes (OR 4.3 [95%CI 3.3 to 5.5]) and still further at 30 minutes (OR 6.2 [95%CI 4.6 to 8.2]). Concluding that the best predictor for PPH using receiver operating characteristic (ROC) curves was 18 minutes (Magann *et al*., 2005b). Earlier work had also identified rapid

placental delivery, with the majority delivered within 15 minutes in a variety of settings (Dombrowski *et al*., 1995; Gulmezoglu *et al.,* 2001; Combs and Laros, 1991)

5) Epidural analgesia has been associated with PPH (Gilbert *et al.*, 1987), but as this tends to be the preferred pain relief option for women undergoing induction or long labours (Roberts *et al.*, 2004; Duff and Sinclair, 2000), it is difficult to ascertain the independent contribution to PPH. Additionally epidural is associated with longer duration of the second stage of labour and instrumental vaginal birth (NICE, 2007), both of which have been associated with increased blood loss. Although one literature review, whilst reporting increased duration of the second stage of labour with epidural analgesia, concluded there was no consensus regarding optimal length and, furthermore, identified a reduction in mid cavity/ rotational forceps deliveries in women with epidurals (Odiho, 2007). Incidence of perineal trauma and PPH have been reported as similar in women with and without epidurals and with early versus delayed pushing in several RCTs (Rogers *et al*., 1999; Fraser *et al*., 2000; Fitzpatrick *et al*., 2002)

6) Raised maternal temperature in labour has been reported in women with epidural analgesia (Lieberman *et al.*, 1997; Odiho, 2007) and is a cardinal sign of chorioamnionitis (Bailey and Steer, 2007), both of which have been implicated as increasing blood loss. Others have described a "normal" physiological 0.3°C increase in temperature during labour (Schouten *et al.*, 2008). Raised maternal temperature may therefore be associated with other intrapartum factors that contribute to PPH. These observational studies and guidelines focused on maternal pyrexia leading to neonatal sepsis, and incidence of PPH was not

reported, despite the known association between chorioamnionitis and PPH, especially at term (Cooke, 2008).

7) Mode of birth has been cited as a key predictor of blood loss. Spontaneous vaginal delivery is associated with the least blood loss, except where mediolateral episiotomies have expedited delivery and soft tissue damage has been sustained (Combs *et al.*, 1991). Instrumental vaginal births are also associated with increased blood loss (Henry *et al.*, 2005;). Elective and emergency CS have variably reported associations with PPH (Waterstone *et al*., 2001; Ford *et al.*, 2007b) with the temporal rise in PPH reported as not being wholly attributable to increased CS rates (Wen *et al.*, 2005).

Labouring and birthing in water has been associated with less blood loss at delivery (Garland and Jones, 1994), but difficulties in assessing blood volume lost in water means this is impossible to confirm, without undertaking pre and postnatal haemoglobin (Hb) assessment. Despite inherent problems in this approach, one study utlising this methodology reported no benefit of water birth in terms of improving postnatal Hb (Bodner *et al.*, 2002) concluding that giving birth in water had no impact on blood loss.

8) Management of the third stage of labour is the term used to describe how the placenta and membranes are delivered and bleeding is controlled. Active management of the third stage of labour (AMTSL) is described as a combination of interlocking interventions, most commonly prophylactic administration of a uterotonic drug, early cord clamping and controlled cord traction (Prendeville *et al*., 2000). Others have included uterine massage and are less prescriptive

regarding timing of cord clamping (WHO, 2000). Several clinical trials have convincingly demonstrated that AMTSL prevents PPH (Prendiville *et al*., 1998; Rogers *et al*., 1998; Prendiville *et al*., 2000) and it is recommended for all women (RCOG, 2002). Due to differences in some aspects of the management in earlier trials, for example dose, route, timing and choice of uterotonic, and 'early' versus 'delayed' cord clamping, there remains less consensus regarding the impact of individual components (Gulmezoglu and Souza, 2003) and insufficient evidence to recommend an optimal uterotonic drug (NICE, 2007).

The origins of 'early' cord clamping are unclear (Weeks, 2007), but it was integral to the protocol for a cohort study investigating controlled cord traction in 1962 (Spencer, 1962). Early cord clamping is not universally adopted (Winter *et al*., 2007). The benefits of delayed cord clamping have long been advocated for preterm infants (Kinwood *et al*., 1993) and more recently a systematic review and meta-analysis in term babies reported delayed cord clamping improved haematologic status in the children when aged 2-6 months (Hutton and Hassan, 2007). Although early cord clamping has been advocated to prevent PPH, a Cochrane Review reported no increased risk of excessive bleeding when cord clamping is delayed by 2-3 minutes (McDonald and Middleton, 2008).

Controlled cord traction (CCT), first introduced in the 1930s, has long been advocated to reduce both PPH and retained placenta (Quadir Khan *et al*., 1997). However this large RCT compared early administration of uterotonic and CCT with no cord traction and administration of uterotonic following delivery of the placenta. The impact of CCT alone cannot therefore be ascertained. More recently a pilot randomized superiority trial where women received intramuscular

uterotonic with birth of the anterior shoulder, regardless of allocation to CCT or hands-off technique,

Similarly, although administration of a uterotonic is considered pivotal in the prevention of PPH, the choice of uterotonic remains controversial. A Cochrane Review concluded that prophylactic oxytocin, as opposed to no uterotonic, reduced blood loss but there was little evidence of any difference in blood loss when oxytocin was compared with ergot alkaloids. However, these were associated with more manual removals of placenta and there was a suggestion of increased hypertension (Cotter *et al*., 2001). Comparison between ergometrine-oxytocin (Syntometrine®) and oxytocin showed that whilst there was a small statistically significant reduction in the risk of PPH with the ergometrine-oxytocin compound this was associated maternal side effects (raised BP nausea and vomiting) (McDonald *et al.,* 2004). Ergot alkaloids (Ergometrine®) administered intramuscularly or intravenously were found effective at reducing blood loss but were associated with elevated blood pressure and severe pain (Liabsuetrakul *et al*., 2007). Whist confirming the effectiveness of a prophylactic oxytocin and ergometrine compound (Syntometrine®) with associated side-effects (most notably hypertension), a further review concluded there was no evidence that intravenous administration of a long acting oxytocin agonist (Carbetocin®) was more effective than oxytocin at reducing PPH (Su *et al*., 2007). Other potential prophylactic uterotonics investigated include oral prostaglandins (Misoprostol®) that have the advantage of requiring minimal storage requirements, but was not more effective than other uterotonics in preventing PPH and was frequently associated with side effects (raised basal temperature, nausea and shivering) (Gulmezoglu *et al*., 2007). More recently tranexamic acid has been proposed as a useful alternative or adjunct to current prophylactic uterotonic drugs having been

shown to reduce blood loss in trauma and surgery. Tranexamic acid is not a uterotonic but an antifibrinolytic and therefore could be particularly useful when PPH is due to placenta praevia or genital tract trauma and has already been shown to reduce blood loss following CS in a randomised controlled trial of primiparous women (Gai *et al*., 2004). A Cochrane Review found that, whilst potentially effective at reducing blood loss, further research is required before it could be recommended in practice (Novikova and Hofmeyr, 2010)

Conversely, proponents of physiological management of the third stage state it is the natural conclusion of a normal labour (Davis-Floyd, 2003) with no resultant adverse consequences, in terms of need for transfusion or increased inpatient nights when used appropriately (Begley, 1990). Although evidence from a randomised controlled trial concedes incidence of PPH> 500 ml is higher and haemoglobin concentration is lower in women who have expectant third stage management (Begley, 1990). Confirming the results from two seminal randomised controlled trials, the Bristol third stage trial (Prendiville *et al*., 1988) and the Hinchingbrooke trial (Rogers *et al*., 1998). The latter acknowledged the importance of staff remaining competent in both management strategies for delivery of the placenta, and also identified the importance women and their health providers place on blood loss following a physiological birth (Rogers *et al*., 1998). These findings were subsequently confirmed in systematic reviews (Prendiville *et al*., 2000; Prendiville *et al*., 2003). But this meta-analysis also concluded that physiological management of the third stage of labour may be appropriate in domiciliary environments (Prendiville *et al*., 2003).

More recently, and in the face of irrefutable evidence for the effectiveness of active management, proponents of physiological management have attributed biomedical domination as underpinning the universal adoption of interventionist

obstetrics, leading to a risk-entrenched approach that has replaced physiological management with comprehensive active management (Fry, 2007). Factors to enhance physiological delivery of the placenta have been identified and include reducing fear, cold and bright lights (Gyte, 2006; Odent, 2003), uninterrupted skin to skin contact and suckling to promote a surge of oxytocin required for placental separation (Page, 2007), no cord clamping as free drainage of placental blood causes the placenta to 'shrink", promotes the effective uterine contractions required and reduced retroplacental blood loss (Lucas, 2006). However none of these processes have been formally tested in randomized controlled trials.

Guidelines state that midwives should remain competent in both methods of placental delivery and control of bleeding (Jokinen and Munroe, 2008; NICE, 2007). Lack of expertise and confidence in either management technique, has been associated with increased blood loss (Rogers *et al*., 1998), with resultant "piecemeal" management cited as additionally causative of retained placenta and uterine inversion (Inch, 1988). An investigation of European policies for third stage management found wide variation in practice (uterotonic agents used, timing of administration, draining of placenta, timing of cord clamping and application of controlled cord traction) and differences in practice and policy documents (Winter *et al*., 2007). This study used postal questionnaires, with wide variation in numbers of both invited respondents (22 - 719 in each country) and response rates (29=100% in each country). The diversity of practice identified in this study, given the documented limitations of postal surveys, in terms of response rates and self selection, could imply even more variation in practice than reported here.

9) Retained placenta has long been identified as a cause of PPH (Al-Zirqi *et al*., 2008; Stones *et al*., 1993). Partial accreta is particularly problematic and associated with the greatest blood loss (Weeks, 2008). Some report manual removal of retained placenta as causative of severe PPH following spontaneous vaginal birth (Hazra *et al.*, 2004). The treatment of retained placenta varies dependent on the cause, but delay can lead to severe morbidity (Chhabra and Dhorey, 2002).

Duration of the third stage was identified as a risk factor for PPH> 1000 ml in a large observational study of women following vaginal birth, with the optimal time to avoid PPH being 18 minutes (Magann *et al*., 2005). This single Centre study employed AMTSL in all women (IM oxytocin with delivery of the anterior shoulder), and manually removed undelivered placentas after 30 minutes. These policies remove maternal choice regarding both physiological management of the third stage, and delaying manual removal of placenta in the absence of bleeding. It was also undertaken in a single Centre which may not be replicated elsewhere. However it is a large study employing meticulous blood loss data. But information regarding the impact of vaginal operative deliveries, although included (incidence 17%), was not reported, neither was the impact of previous history in multiparous women who constituted 55.2% of the study population.

10) Episiotomy has been shown to be a major cause of severe PPH following instrumental vaginal birth, with second and third degree tears more frequently causative following spontaneous vaginal birth (Hazra *et al.*, 2004). Although historically undertaken to expedite birth and prevent vaginal tears, research

emerging in the 1990s showed episiotomy did not reduce perineal trauma or birth asphyxia and was associated with PPH (Cleary-Goldman and Robinson, 2003). A randomised controlled trial of routine (all cases) versus restrictive (only performed with evidence of tearing) episiotomy, reported a moderate increase in PPH (>500 ml) in the routine episiotomy group (Murphy *et al.*, 2008). Given the decreasing incidence of episiotomy, at a time of increasing PPH, the impact of this surgical procedure could be considered less important than when it was undertaken more routinely.

This survey of the available evidence the complexity of risk factors is apparent and concurs with the National Institute of Health and Clinical Excellence (NICE), which also reported widely varying degrees of evidence for risk factors for PPH, and concluded that production of an exhaustive list was not possible (NICE, 2007). The factors identified by NICE are shown in Figure 2.4. NICE recommendations included counseling regarding place of birth and an identified documented care plan for women with identified risk factors. No comment regarding the cumulative impact of multiple risk factors was made and risk factors were not ranked depending on impact. Most risk factors have been identified though retrospective coded data, cross sectional, cohort and observational studies. This means most of these findings lack a control or comparison group and therefore the level of evidence is less than ideal.

- **Antenatal risk factors:**
  - Previous retained placenta or postpartum haemorrhage
  - Maternal haemoglobin level below 8.5 g/dl at onset of labour
  - Body mass index greater than 35 kg/m²
  - Grand multiparity (parity 4 or more)
  - Antepartum haemorrhage
  - Overdistention of the uterus (for example, multiple pregnancy, polyhydramnios or macrosomia)
  - Existing uterine abnormalities
  - Low-lying placenta
  - Maternal age 35 years or older.

- **Risk factors in labour:**
  - Induction
  - Prolonged first, second or third stage of labour
  - Oxytocin use
  - Precipitate labour
  - Operative birth or caesarean section.

Figure 2.4: Risk factors for PPH identified by NICE (NICE, 2007)

2.2.5 The Impact of PPH

2.2.5.1 Mortality versus morbidity

Whilst PPH is responsible for an estimated 125,000 maternal deaths worldwide each year, as previously described such deaths are rare in resource rich countries (Khan *et al*., 2006). In the UK, whilst not always the main cause of maternal deaths, PPH has been consistently cited in the triennial Confidential Enquiry into Maternal Deaths since its inception (Lewis, 2003).

Maternal morbidity is traditionally defined as "morbidity in a woman who has been pregnant (regardless of site or duration of pregnancy), from any cause related to, or aggravated by, the pregnancy or its management, but not by accidental or incidental causes" (WHO, 1990a). Limitations of this definition include consideration of ongoing pregnancies and the lack of clarity regarding duration of the postnatal period. It also lacks the differentiation and classification as described by direct and indirect causes of maternal deaths, outlined in the Confidential Enquiry (Lewis, 2007b).

Although there are wide variations in estimates, it is acknowledged that globally up to 10,000,000 women live with the short and long term health and social consequences of pregnancy complications (UNICEF, 2008) with severe PPH a major cause of these morbidities (Khan *et al.*, 2006). Figure 2.5 depicts the continuum between health and death (adapted from Minkauskiene, 2003). It graphically represents that women can experience an uncomplicated pregnancy and remain well throughout. Others develop a complication that can deteriorate further, from which they either recover completely, or survive with an associated short or long term morbidity. Conversely the complication can deteriorate further and become life threatening, from which the woman may die or will survive but almost certainly sustain a short or long term morbidity. Maternal morbidities associated with PPH include, adult respiratory distress syndrome, coagulopathy, loss of fertility and pituitary necrosis (Abalos, 2009), with their inherent short and long term health, social and societal consequences.

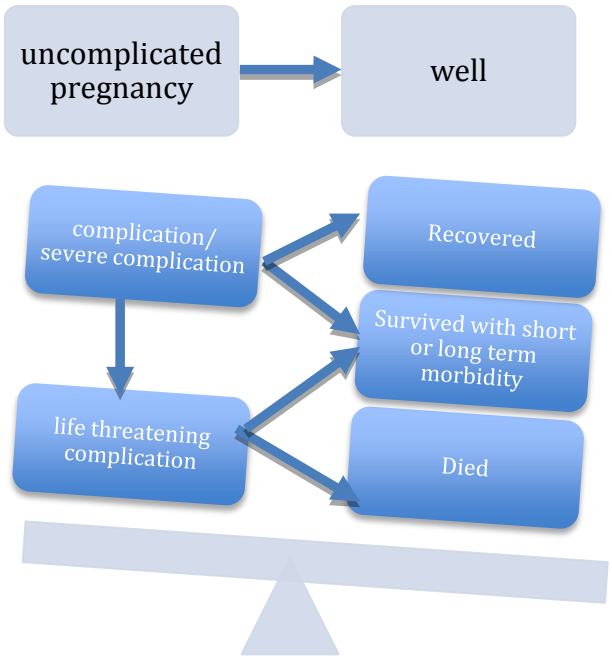


Figure 2.5: Graphic representation of continuum between health and death (adapted from Minkauskienne, 2003)

The impact of morbidities associated with PPH is difficult to establish in the literature. A European Union (EU) collaboration was established in an attempt to monitor and evaluate maternal morbidity using consensus indicators as a composite measure of severe obstetric morbidity. This was considered effective in accounting for virtually all the factors that constitute severe maternal morbidity, regardless of individual member States' maternity service provision (PERISTAT, 2003). One, or more, of the following fulfilled the criteria for the composite measure: eclamptic fit; surgery (except tubal ligation or CS); embolisation; blood transfusion; and intensive care unit admission exceeding 24 hours (Buitendijk *et al.*, 2003). However, evidence should be considered with caution, as the 2008 report referred to data collected in 2003, during the intervening years the EU population increased and evolved, with changing patterns of migration within the community (EUROPERISTAT, 2008).

The impact of PPH as a severe maternal morbidity has been investigated and confirmed; a study in high-income countries concluded that rates of severe maternal morbidity vary between 3.8 and 12 per 1000 births, PPH being the most common cause (van Roosmalen and Zworst, 2009). Disparity in definition and recording and coding issues made data comparison difficult (for example, in Scotland haemorrhage ranked first, compared to 4th in the Netherlands where, intensive care unit admission was first). The potential for under-reporting, due to differences in health systems, variation in definitions and a tendency to underestimate blood loss in particular, for fear of recriminations and accusations of poor practice, was highlighted (van Roosmalen and Zworst, 2009).

A UK population based study of all 229 consultant-led maternity units, found that for every women who died following peripartum hysterectomy (most commonly undertaken to control postpartum haemorrhage) 150 survived with associated consequences (Knight, 2007). These findings confirm the contribution of PPH to the severest acute maternal morbidity in high resource settings. Furthermore it highlights the importance of data consistency and the accuracy of information regarding short and long term effects and subsequent health.

Post-traumatic stress disorder (PTSD) has been associated with childbirth, especially following an adverse event, and investigation of short and long term mental health issues, in addition to social functionality and adaptation to parenthood, have been identified as requiring further investigation (Ayers *et al*., 2008).

2.2.5.2 Near-miss audit

The term "near-miss" was adopted from the aviation industry, where it describes a near accident, without casualties or material damage (Mantel *et al.*, 1998). It therefore does not readily translate to the context of maternal health, where there has already been an "accident" with a "casualty" and the prospect of short and long-term consequences, "material damage". Furthermore the definition of "near-miss" depends on local facilities and maternal health parameters, but the originator of the term, defined a "near-miss" event as: " a very ill woman who would have died, had it not been that luck and good care were on her side" (Mantel *et al.*, 1998; Bewley and Creighton, 1997). The inclusion of "good luck" before "good care" in this definition, as requisite to survive such an event is curious. The term "near-miss" effectively evokes emotions regarding the seriousness of the situation, but the term severe acute maternal morbidity (SAMM) is preferred by others, avoiding the inherent ambiguity caused by translation from the original context (Zwart *et al.*, 2008).

The ten-fold reduction in the UK maternal death rate between 1952 and 2002 (530 to 53 per million maternities) indicates that death is too rare an event to be a sensitive marker of quality of care. Other high-income countries have also achieved dramatic reductions in maternal deaths and therefore severe acute maternal morbidity (SAMM), or "near-miss" audits, have been advocated as useful mechanisms to examine practice and improve patient care, providing a valuable quality indicator for obstetric services and a useful adjunct to the Confidential Enquiries into Maternal Deaths (Hill *et al.*, 2007; Lewis, 2007a; Drife, 1993). The impact of examining critical incident audit in maternity and perinatal health has not been evaluated in randomised controlled trials (Pattinson *et al.*,

2005), but review of observational data relating to near-miss events around PPH, concluded that despite diverse approaches, and varying inclusion criteria (Penney and Brace, 2007; Baskett and O'Connell, 2005; Mantel *et al.*, 1998; Stones *et al.*, 1991), this form of analysis was effective in identifying suboptimal care and should be accepted as complementary to maternal mortality reports (Penney and Adamson, 2007a). Objective assessment of severity of morbidity remains challenging with incidence dependent on definition, and management dependent on availability of health care resources, in addition to maternal health status prior to the insult.

Despite reported advantages in critical incident analyses to identify and address suboptimal care, the effectiveness of this type of investigation is dependent on standardisation of frameworks used, identification of robust "triggers" for action and acknowledgement of the influence of human error in these events, with supportive and non-punitive treatment of those involved (Kershaw, 2007;Iedema *et al.*, 2006; Ahluwia and Marriott, 2005). In qualitative studies doctors have been identified as particularly reluctant to report critical incidents, believing that errors are "inevitable", fearing retribution or failure and investigation by "non-medical" professionals. All further compounded by anti-bureaucratic sentiment and desired avoidance of excessive administrative work (Waring, 2005; Lawton and Parker, 2002). This may be due, in part, to the lack of reflexivity in their training and perceived lack of support (Vincent *et al*., 1999). Nurses, on the other hand, have been identified as more likely to report such incidents (Throckmorton and Etchegaray, 2007; Meurier 2000). Although the largest of these studies was undertaken in USA and organisational differences in health delivery may mean the findings are not transferable (Throckmorton and Etchegaray, 2007). Investigations in other clinical areas have used different critical analyses

techniques, and have advocated their implementation in other areas of medicine (Tighe *et al*., 2006) but with different models employed it is difficult to draw conclusions as to which might be most effective in any given area. Indeed, in the UK, Woloshynowych and colleagues identified the further potential for development of novel techniques and transfer of others from high risk industries to better utilise critical incident analysis to improve patient care; but cautioned the need for these implementation of recommendations to be formally evaluated (Woloshynowych *et al*., 2005)

Table 2.4 shows several epidemiological and register studies have reported marked increases in maternal morbidity in high income countries, regardless of definitions used, possibly due to changes in the demography of childbirth (Zwart, 2009).

Table 2.4: Summary of epidemiological and register data demonstrating increased maternal morbidity in high income countries over time (Zwart 2009, p167**).**

Country	**Time period**	**Rate of SAMM per 1000 births**	**Increase**
Canada	1991- 1993	4.6	
(Wen *et al.,* 2005)	1998- 2000	4.6	0%
Finland	1997	5.9	
(Pallasmaa *et al*., 2008)	2002	7.6	29%
USA	1991-1994	4.3	
(Callagan *et al*., 2008)	1995-1998	5.9	31%
USA	1998-1999	6.4	
(Kuklinger *et al.*, 2009)	2004-2005	8.1	27%
Australia (NSW)	1999	11.5	
(Roberts *et al.*, 2008)	2004	13.8	21%

Footnote: SAMM: Severe Acute Maternal Morbidity. NSW: New South Wales.

Wen and colleagues (2005) demonstrated how PPH and uterine rupture were more common than other severe acute maternal morbidities in Canada between 1991 and 2000, shown in Figure 2.6. The apparent reduction in PPH rates is misleading, as the definition relied on receipt of blood products, and the threshold for transfusion changed significantly during this decade (Wen *et al.*, 2005).

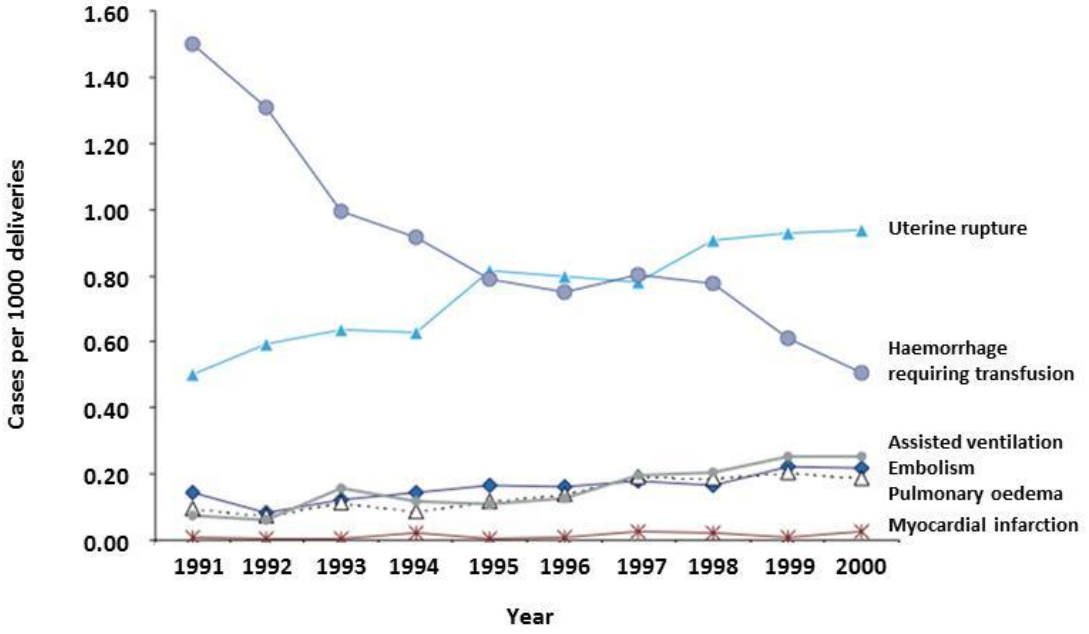


Figure 2.6: Data illustrating severe postpartum haemorrhage (requiring transfusion), and uterine rupture as major causes of severe acute maternal morbidity SAMM (Wen, 2005 p Online-4).

Consecutive Scottish Audits of Maternal Morbidity have consistently reported massive obstetric haemorrhage (MOH) as the major cause of severe morbidity. In the 2005 report this accounted for 75% of all "near-miss" events (Lennox and Marr, 2007) and 74% in the 2008 audit (Lennox and Marr, 2010). This is depicted in Figure 2.7, visually demonstrating the impact of obstetric haemorrhage.

A large Irish cohort reported incidence of severe acute maternal morbidity in 2003-2004 as 3.2/1000 maternities. Vascular dysfunction following major obstetric haemorrhage was the most common cause (36%) (Murphy *et al.*, 2009). These data confirm the impact of PPH on maternal morbidity in many high income countries, with abundant resources to deal with severe bleeding.

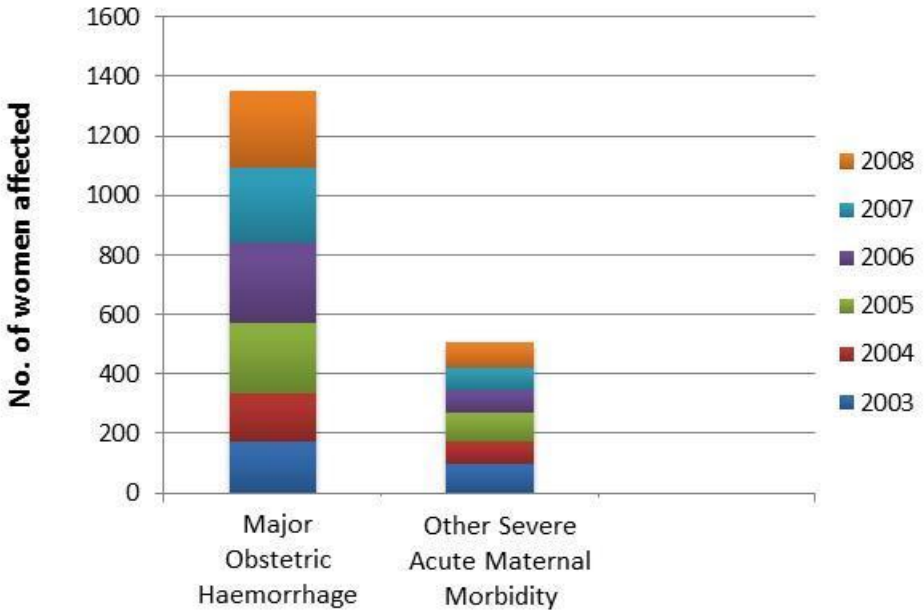


Figure 2.7: Severe acute maternal morbidity, displayed cumulatively year on year between 2003-2008 to compare contribution of major obstetric haemorrhage (MOH) with all other severe acute maternal morbidities (SAMM) (adapted from Lennox and Marr, 2010).

In addition to the consequences for the women, there is an inherent demand on resources in dealing with PPH. The UK Intensive Care National Audit and Research Centre reported PPH was the most common cause of admissions of "recently pregnant" women (ICNARC, 2009) accounting for 34% of admissions. This refers to seriously ill women admitted to adult general intensive care units (ITU). Therefore it is likely to be an underestimate of the impact of PPH, as many maternity units now have high dependency areas where recently delivered ill women are cared for within maternity services. In the Scottish Confidential

Audit, 42 of the 90 women (46%) admitted to ITU experienced PPH (Lennox and Marr, 2010). Similarly this is likely to be an underestimation, as not all maternity units in Scotland have access to ITU, further demonstrating that any definitions or management strategies may be more representative of resource availability and clinician preference than severity of maternal condition.

These data confirm that PPH remains a major complication of childbirth in high-income countries, despite heterogeneity of definition, differences and limitations of documentation, resource differences and advances in clinical practice. It also shows the benefit of audit in ascertaining practice, identifying and promoting good care, whilst identifying and addressing substandard care. PPH has inherent personal, medical and societal impacts in terms of health and wellbeing, as well as concomitant financial and other resource implications to the NHS, social care, education and individuals.

2.2.6 Assessment of blood loss

Ambiguity around assessment of blood loss at birth has long been contentious being regularly criticised as unreliable and ineffective (Bose *et al*., 2006; Prasertcharoensuk *et al.*, 2000; Newton *et al.*, 1961). Early textbooks typically advised postpartum blood loss was recorded as "small/minimal", "average/moderate" and "large/heavy/excessive" (Luegenbiehl *et al.*, 1990).

Blood loss at birth, and in the early postnatal period, is most commonly assessed visually, by attending clinicians facilitating the birth and providing early postnatal care. Training tends to be minimal and most commonly undertaken at the bedside (Stafford *et al.*, 2008). Visual assessment has been associated with both under- and over-estimation (Bose *et al*., 2006; Dildy *et al.*, 2004; Higgins, 1982) and variably associated with mode of birth (Larsson *et al.*, 2006). The proportion of underestimation has been reported as 33-50% when compared to photospectrometry and colorimetric measurement of alkaline hematin in blood, which are considered the "gold standard" for blood loss assessment (Patel, 2006a). Using simulator training, similar levels of under-estimation have been reported in Australia (Glover, 2006), USA (Dildy *et al*., 2004) and the UK (Bose *et al*., 2006). Prasertcharoensuk and colleagues (2000) reported visual assessment leading to underestimation of PPH (>1000 ml) by 88.9% when compared with direct measurement. An additional meta-analysis also discovered that when blood loss was measured the incidence of PPH was 10.5% compared with 7.2% when blood loss was assessed visually (Carroli *et al.*, 2008). This considerable underestimation of blood loss artificially reduces the reported incidence of PPH.

Others have applied complex formulae to calculate blood loss volume (calculated pregnancy volume [0.75 x maternal height in inches x 50] +[maternal weight in pounds x 25] x % blood volume lost [predelivery haematocrit - postdelivery haematocrit/predelivery haematocrit]) and compared this with visually estimated blood loss (Stafford *et al*., 2008). These authors concluded that when visual assessment alone is used blood loss is significantly underestimated and that further adjustment was required depending on perineal trauma sustained. Implementation of this calculation is less burdensome, yet provides comparable

results to those of more robust laboratory investigations reported in early seminal papers (Pritchard, 1965).

The ability of attending clinicians to accurately assess blood loss in obstetrics and emergency medicine has been variably reported in the literature. Some suggest that estimation of blood loss is so poor that patient management should be dictated by vital signs, symptoms of shock, mechanism of injury and associated comorbidities rather than estimated blood loss (Tall *et al*., 2003; Patton *et al*., 2001). Direct comparison with emergency medicine may not be appropriate as major blood loss is commonly associated with multiple injuries, requiring independent and targeted treatments. Additionally physiological adaptations to pregnancy mean that early postnatal women compensate for blood loss differently to trauma victims.

Kavle and colleagues (2006) compared visually estimated blood loss with quantified methods using alkaline hematiin and reported midwives assessment as within 5 ml of the more robust assessment (Kavle *et al*., 2006). Greater differences were seen when visual assessment exceeded 200 ml, concurring with others that lower levels of blood loss are more accurately assessed than larger volumes (Schorn, 2008). Kavle's study is preliminary work in an affluent area of a developing country and may have been influenced by the provision of free safe birth kits and local sociodemographic factors, therefore potentially of questionable generalisability. All blood loss was significantly lower than that reported in an early US cohort utilising a similar method, despite no prophylactic uterotonic, other than early breast feeding (Newton *et al*., 1961).

It has been suggested that historically a documented PPH ≥500 ml was considered problematic, prompting rapid response (Myles, 1985). The increase in estimated and documented blood volume lost following birth has been attributed to raised awareness caused by the introduction of obstetric emergency training, with staff are inclined to document higher levels of blood loss (Buckland and Homer, 2007; Black and Brocklehurst, 2003). Classic early studies using robust measurement techniques concluded that, regardless of visually estimated volumes, average post birth blood loss was 500 ml and 7% of women lost ≥1000 ml (Pritchard, 1961). Thus, it could be argued that historically health care practitioners were more likely to underestimate blood loss, a situation that is, to some degree, less apparent today. Unfortunately, it is difficult to ascertain the contribution of this practice change to the increasing reported trend on PPH.

Whist visual estimation remains acceptable for smaller volumes of blood loss, once excessive bleeding is recognised weighing of swabs and drapes (gravimetric methods) in addition to frequent biochemical assessment to monitor and inform treatment is required (RCOG, 2009; Brace *et al*., 2007; Stainsby *et al*., 2006).

Failure to accurate record blood loss has been associated with substandard care identified in maternal mortality and morbidity reports (Lewis, 2007; Brace 2007).

The collection of blood directly into receptacles was also advocated, but was only achievable when women gave birth in a static supine position (Newton *et al.*, 1961). Other gravimetric techniques, such as drape estimation and the use of calibrated and non-calibrated plastic collector bags are alternative measurement approaches, which demonstrate greater accuracy. However, to date, these have

failed to be widely adopted (Patel *et al.*, 2006b; Alexander *et al.*, 2005) outside the domain of operative birth (Stafford *et al.*, 2008). This may be due to criticism that these tools fail to discriminate between blood and other body fluids and inhibit maternal mobility during labour (Alexander *et al*., 2005). Furthermore, some have suggested that the specific construction materials used, and the presence of clots, may affect the accuracy of blood loss measurement with these tools (Patel, 2006a).

Photometric methods and radioactive chromium-tagged red blood cell techniques have long been advocated as more accurately assessing blood loss (Chua *et al.*, 1998; Gahres *et al.*, 1962). Unfortunately, these are not practical in the clinical situation, due to the time taken causing treatment delay in addition to cost constraints. There are also limitations to comparing antenatal and postnatal haematocrit, which additionally has been shown to correlate poorly with visual estimation of blood loss. When blood loss is normal (<500 ml) haematocrit levels commonly remain unchanged, or even elevated (Gharoro and Enabudoso, 2009), thus rendering this clinically unusable for several reasons.

2.2.6.1 Strategies to improve estimation of lost blood volume

Staff training in obstetric emergencies, including PPH has been strongly advocated (Crofts *et al.*, 2007). The Confidential Enquiry into Maternal and Child Deaths and the Confidential Enquiry into Stillbirths and Deaths in Infancy have long recommended training drills to reduce substandard care and enhance staff

confidence (Lewis and Drife, 1998; Lewis 2003). Additionally, the Clinical Negligence Scheme for Trusts (CNST) insists that 'all relevant staff annually participate in skills drills' training to qualify for Level 2 status (Clinical Negligence Scheme for Trusts, 2003), further confirming the belief that skills and drills training is an essential requirement to reduce morbidity and develop and maintain staff competence. However evidence exists that, whilst some training courses are effective at increasing staff knowledge, there is no resultant improvement in patient care (Black and Brocklehurst, 2003).

Clinical reconstructions, implementation of guidelines and staff education have been promoted to improve visual estimation of blood loss and prompt recognition of excessive bleeding (Bose *et al.*, 2006; Rizvi *et al.*, 2004). Practical simulations (drills and skills) have been shown to be more effective in increasing and retaining knowledge than didactic lectures or a combination of lectures and practical sessions (Buckland and Homer, 2007). Potentially because simulation-based learning exposes learners to events, in a safe, controlled environment. This is consistent with the constructivist learning principles that promote retention, understanding and active use of skills (Lathrop *et al.*, 2007).

The pivotal role of effective teamwork, and resultant importance of multidisciplinary training in obstetric emergencies is acknowledged (Neilsen *et al.*, 2007). Additionally the reflective techniques widely used in midwifery and medical education maximise the effect of this type of learning but, with reflexivity being an integral part of simulation-based learning post training support must be available to maximise the benefits of this type of learning (Lyons, 1999).

Common errors occur repeatedly around obstetric emergencies, in PPH these are identified as: 1) failure to transfer bleeding patients to operating theatres, 2) unfamiliarity with drug regimes to correct uterine atony, and 3) poor cardiopulmonary resuscitation techniques (Maslovitz *et al.*, 2007). This seems to reiterate the importance of promptly recognising excessive bleeding, dealing with it in an appropriate setting and being confident and competent in all aspects of resuscitation. Disappointingly, the evidence suggests that whilst various techniques to improve estimation of blood loss, and emergency training have emerged and been adopted, the outcomes of PPH remain unchanged (Bose *et al.*, 2006; Black and Brocklehurst, 2003). It has been reported that where awareness of PPH is high and consequent training and management standardised, it is still difficult to correlate individual training directly with outcome (Zhang *et al.*, 2010). Suggesting that improved estimation and assessment of blood loss does not improve outcomes.

2.2.7 The impact on those involved

2.2.7.1 Women, birth partners and staff

There is an emerging literature regarding the development of post traumatic stress disorder (PTSD) in those who have experienced traumatic birth events (Beck, 2004; Bailham and Joseph, 2003). The subjectivity of trauma perception is noted, as is the impact of support during such events (Seng *et al.*, 2001), and the effect on birth partners and couples who experience near miss events (Nicholls, 2007). The requirement for future research in this area and construction of diagnostic and conceptual frameworks is identified (Ayers *et al.*, 2008). Increased stress levels in men witnessing traumatic birth events have

been reported (Somers-Smith, 1999) and further corroborated by a healthcare professional who stated normal birth can lead to paternal depression. This phenomenon is reportedly multiplied when men witness adverse events (Odent, 2008; Schumacher *et al.*, 2008). Whilst uncertainty exists around the manifestations, longevity, effects and management of this condition, there is unanimous agreement that women and their birth partners can experience PTSD following near-miss events and this adversely impacts on their health and confidence in parenting, with concomitant longer term health and social issues for the family (Gamble *et al.*, 2000; Axe, 2000; Alexander, 1999).

The importance of early contact and bonding between parents and child is acknowledged as fundamental for successful long term parenting. Parent-child bonding can be reduced when mothers suffer ill health around giving birth, subjecting the child to adverse psychological affects throughout life (UNICEF, 2004). Exclusive breast feeding is the optimal infant diet for the first six months of life (WHO, 2009a). Initiation and establishment of lactation is more difficult following adverse intrapartum events, and crucially women requiring emergency treatment may be separated from their baby for prolonged periods in the first day of life further impairing the initiation of breast feeding (UNICEF, 2004). Postnatal low haemoglobin levels are associated with maternal symptoms of fatigue, fainting, dizziness (Glazener *et al.*, 1993) slower recovery from childbirth (Waterstone *et al.*, 2003) and the introduction of infant formula feed due to inadequate lactation (UNICEF, 2004). Babies given formula feeds in the early postnatal period are less likely to subsequently succeed at breast feeding (WHO, 2009a). Consequently experiencing PPH with concomitant issues inhibits adaptation to life as a new, or larger, family.

The Care Quality Commission (formally the Health Care Commission) reported a high level of complaints from women and their families relating to emotional as well as physical suffering following PPH (Sue Eardley, RCM Conference presentation, Brighton, 2008).

At the time of embarking on this work, there was a paucity of evidence regarding the effect on staff of dealing with obstetric emergencies, the most common of which is PPH, although there was growing evidence of the impact of vicarious trauma on other health care professionals (Jonsson and Halabi, 2006; Sluiter *et al.*, 2003). Given the unique and distinct close woman-midwife relationship it is hypothesised that midwives may be at particular risk of suffering emotional distress as a result of involvement in traumatic events (Carolan and Hodnett, 2007).

2.2.7.2 Economic impact of PPH

No formal evaluation of the health care resource costs have been undertaken in relation to PPH, potentially due to difficulties in attributing ongoing health and social care needs to PPH, as opposed to other aspects of childbirth.

According to the Department of Health (DOH) website, inpatient hospital bed days cost £400 (www.doh.gov.uk/stats downloaded 6th May 2010); a medical consultation £250-400; a standard unit of packed cells £130.52, rising to £213.79 for platelets (www.nbt.nhs.uk/recruitment/documents downloaded 6th

May 2010). Other costs are difficult to acquire, but even this simple example shows PPH confers considerable financial burden on the NHS.

Financial implications for the family are not inconsiderable when considering loss of earnings due to prolonged care requirements or delay in return to work and additional transport or childcare costs. It is difficult to envisage how these costs could be accurately assessed in a local, regional or national level, although they must be considered significant.

2.2.8 Management debate including prevention

2.2.8.1 Evolution of the management of the third stage of labour

As outlined in Chapter 1, arresting excessive bleeding following birth has been documented through the ages. According to the Ebers Papyrus (1500BC) the Ancient Egyptians used fly excrement, juniper berries, celery in milk or hemp in honey, to ameliorate blood loss (Nunn, 1996). They also tied weights to the umbilical cord and encouraged women to sneeze to expedite placenta delivery (Gulmezoglu & Souza, 2009).

By the 18th century the association between haemorrhage, uterine atony, hypovolemic shock and maternal death was well described in a case notes of a leading obstetrician (Smellie, 1752).

The original modern oxytocic drug was a fungus called ergot. There were epidemics of ergotism, a condition caused by eating rye bread contaminated with the fungus, and related to wet seasons and damp crops when the fungus flourished. It was noted that during these epidemics women miscarried and midwives therefore concluded that ergot caused uterine contractions. Adam Lonicer first reported the effectiveness of ergot in inducing uterine contractions in his herbal book published in 1582. It was more than 200 years later that the effects of ergot were first reported in a medical journal (Paulitsky, 1787 cited by Nunn, 1996). Early case reports appeared in the literature advocating the use of ergot to expedite labour and control postpartum bleeding (Stearns, 1808). However by 1822 the association of premature ergot use and fetal or neonatal demise were reported (Stearns, 1822) and as a result the role of ergot was promoted solely for treatment of PPH . By the late 19th and early 20th century numerous scientists were developing increasingly sophisticated products to enable dose titration and therefore increase safety (Hart, 1912). The first clinical trial of Ergotine versus breast feeding to cause uterine contractions was undertaken in 1932 (Moir, 1934).

In 1953 Vincent Du Vigneaud identified the structure of oxytocin and synthesized the hormone, revolutionising the active management of the third stage of labour (Du Vingneaud *et al*., 1953).

Early studies prospectively evaluating the benefits of components of the third stage of labour versus physiological or expectant management were undertaken in the 1980s and 1990s advocated AMTSL as reducing blood loss and shortening the duration of the third stage, although resultant reduced neonatal packed cell volume was identified (Prendiville *et al*., 1988; Nordstrom *et al*., 1997; Rogers *et al*., 1998).

Other studies investigated the impact of oxytocin and oxytocin and ergometrine (Mitchell and Elbourne, 1993); this RCT concluded that, whilst there was no difference in duration of third stage or manual removal of placenta, combined oxytocin and ergometrine (Syntometrine®) led to less PPH >500 ml, but was associated with hypertension, nausea and vomiting.
A Cochrane review in 2000 stated conclusively that AMTSL was associated with less blood loss and fewer postpartum complications than physiological management, however the prophylactic uterotonics varied and therefore no conclusions could be made regarding the most effective drug (Prendiville *et al*., 2000).

A later prospective study in Japan suggested that intramuscular oxytocin caused less mean blood loss than intramuscular ergometrine, and halved the risk of PPH ≥500 ml (Saito *et al.,* 2007). Women were allocated temporally to treatment allocation, which would appear less rigorous than randomization and indeed there were disproportionate numbers in each arm. Additionally blood loss was only assessed up to 12 hours post delivery, thus not conforming to the WHO definition of PPH, which includes all blood loss in the first 24 hours following birth (WHO, 1989).

Other components of the package of interventions constituting active management of the third stage of labour have been previously outlined in Chapter 1, and discussed in Management of the third stage earlier in this chapter (p73). Following review of an historical medical textbook series Aflaifel and Weeks (2012) developed a timeline of the evolution of medical education regarding third stage management practices since 1917 to 2011, this is shown in Figure 2.8.

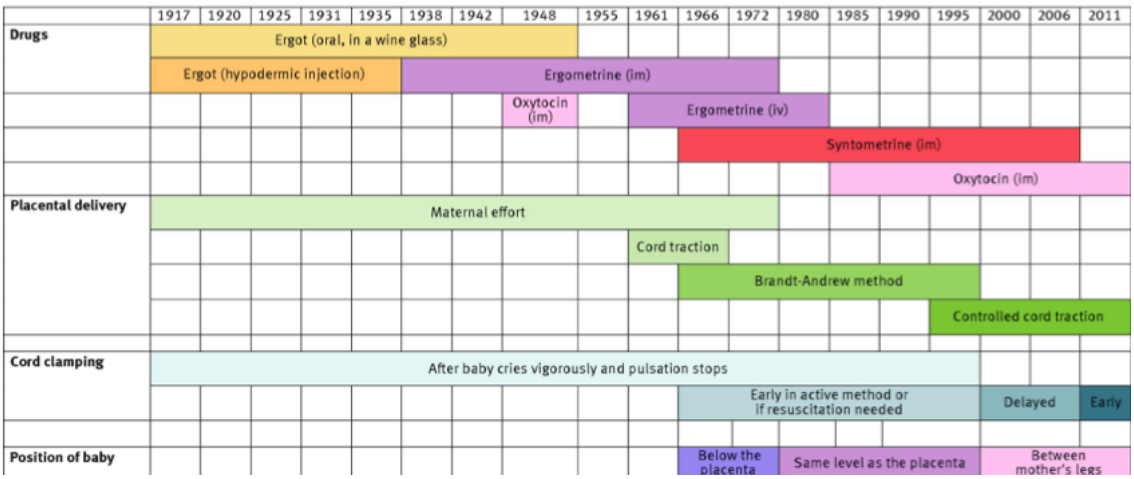


Figure 2.8: Routine management of the third stage of labour. Intramuscular IM, intravenous IV (Aflaifel and Weeks, 2012)

Figure 2.8 clearly shows that the administration of uterotonic drugs has been consistently recommended, but controlled cord traction and early cord clamping are relatively new innovations.

Despite PPH being long identified as problematic and the discovery of medicines and evolution of care, much uncertainty exists around the impact of individual components and it is widely acknowledged that many women receive "piecemeal" management of varying quality.

2.2.8.1 Identification of those at risk

Despite many identified associated risk factors PPH is frequently an unexpected event (Walfish *et al.*, 2009). Conversely positive risk assessment does not always correctly predict haemorrhage (Devine and Wright, 2009). Despite this unpredictability many protocols state that women with identified risk factors should be aware of the potential for PPH and an appropriate care pathway be designed and adjusted in response to the emergence of risk factors (Arulkumaran *et al.*, 2009; NICE, 2007).

2.2.8.2 Standardisation

The introduction of guidelines and protocols is advocated as essential to standardise and improve patient care. Standardisation of definitions used in obstetrics has been recommended (Thevakumar *et al.*, 2008) and minimum standards of care have been created (Whittle, 2007). The value of clinical care guidelines have been outlined and developed in various aspects of pregnancy related care (NICE, 2008a; NICE, 2007; RCOG, 2004; RCOG, 2002) including the intrapartum period (RCOG, 2009; NICE 2008b; NICE, 2007). Early midwifery textbooks commonly advocated categorisation of blood loss was reported (minimal, average/moderate or large) (Neeson and May, 1986; Myles, 1985). Subsequently the value of quantified volumes was acknowledged (Luegenbiehl *et al.*, 1990) but despite several attempts standardisation, or reproducible, accurate assessment, has not yet been achieved (McConnell *et al.*, 2007; Kodkany and Derman, 2006; Kavle *et al*., 2006).

In accordance with guidelines (Arulkumaran *et al.*, 2009) maternity services have protocols for the prevention and management of PPH. Approaches introduced to standardise care include guidelines implementation (RCOG, 2009) and evidence based multi-methods training packages incorporated into mandatory training for all clinical staff (Johanson *et al.*, 2002).

Increased awareness of PPH in developed countries has reportedly resulted in routine approaches to care (WHO, 2006b; ACOG). Despite this, and the implementation of evidence based protocols for the prevention and treatment of PPH, there remains lack of consensus and local, regional and national variations in practice (Knight *et al.*, 2009; Winter *et al.*, 2007 Cameron *et al.*, 2007; Mousa and Alfirevic, 2002).

The evidence base for some practices incorporated into guidelines appears unclear. For example, a Cochrane review concluded that whilst uterine massage reduced blood loss after placental delivery, the value of sustained uterine massage, with and without uterotonics, could not be assessed (Hofmeyr *et al.*, 2008). Conversely, there is good quality evidence that active management of the third stage of labour reduces blood loss, but most units have protocols for physiological management of the third stage (Prendiville *et al.*, 2000), Additionally there is variation regarding components of active management, particularly around the uterotonic of choice, timing of uterotonic administration (with birth of the anterior shoulder/following expulsion of the child), timing of cord clamping and inclusion of placental drainage. This variation was highlighted in a European wide study and is summarised in Table 2.5 (Winter *et al.*, 2007).

Table 2.5: Policies for the management of the third stage of labour following vaginal birth in maternity units from 14 countries

(Winter *et al*., 2007 p 848)

	All units replying, *n*	Timing of cutting and clamping cord			Controlled cord traction, *n* (%)	Administration of prophylactic uterotonics, *n* (%)	Active management,** *n* (%)	Draining the placenta, *n* (%)
		Immediately after birth, *n* (%)	After the cord stops pulsating, *n* (%)	Other and not stated,* *n* (%)				
Austria	33	5 (15)	23 (70)	5 (15)	7 (21)	18 (55)	1 (3)	1 (3)
Belgium	105	92 (88)	11 (10)	2 (2)	45 (43)	93 (89)	36 (34)	34 (32)
Denmark	23	4 (17)	17 (74)	2 (9)	5 (22)	13 (57)	2 (9)	1 (4)
Finland	33	9 (27)	23 (70)	1 (3)	7 (21)	29 (88)	4 (12)	2 (6)
France	109	98 (90)	7 (6)	4 (4)	24 (22)	104 (95)	22 (20)	7 (6)
Hungary	98	20 (20)	66 (67)	12 (12)	12 (12)	89 (91)	5 (5)	3 (3)
Ireland	22	16 (73)	5 (23)	1 (5)	21 (95)	22 (100)	17 (77)	3 (14)
Italy	215	142 (66)	43 (20)	30 (14)	28 (13)	197 (92)	20 (9)	14 (7)
Netherlands	91	67 (74)	21 (23)	3 (3)	41 (45)	86 (95)	33 (36)	0 (0)
Norway	46	11 (24)	30 (65)	5 (11)	18 (39)	33 (72)	5 (11)	7 (15)
Portugal	37	33 (89)	1 (3)	3 (8)	19 (51)	31 (84)	13 (35)	9 (24)
Spain	53	40 (75)	7 (13)	6 (11)	13 (25)	45 (85)	7 (13)	8 (15)
Switzerland	68	47 (69)	10 (15)	11 (16)	31 (46)	60 (88)	25 (37)	2 (3)
UK	242	186 (77)	31 (13)	25 (10)	210 (87)	232 (96)	182 (75)	8 (3)

*some units had more than one 'usual' policy or had a policy of cutting the cord 'at another time'
**Usually cut the cord immediately after birth or after the cord stops pulsating, perform 'controlled cord traction' and administer prophylactic uterotonics.

The WHO recommend all women are offered oxytocin 10 IU either IM or IV as the uterotonic of choice, in preference to ergot alkaloids or misoprostol because of lower associated adverse reactions (Gulmezoglu and Souza, 2009). UK guidelines concur with the use of oxytocin but the dose (5 to 10 IU) and administration route are variable (IM, IV, bolus, slow infusion) and other uterotonics are not excluded (Arulkumaran *et al.*, 2009; NICE, 2007).

Therefore whilst active management of the third stage is advocated to reduce blood loss following childbirth (NICE, 2007; WHO, 1990; Prendiville *et al*., 1988; Rogers *et al.,* 1988), the individual contribution of each component and variation of components remains debated (Winter *et al.,* 2007).

2.2.8.3 Treatment of PPH

In principle strategies for the management of PPH remain consistent (RCOG, 2009; NICE, 2007): Immediate treatment– summoning help, uterine massage and IV fluids. The choice of crystalloid or colloid remains contentious (Wise and Clark, 2008) but rapid hydration is essential to maintain maternal circulation. Support refers to allocating a team member to maintain constant communication and support for the woman and her partner throughout the event (NICE, 2007).

Available treatments include: uterotonic options- repeat oxytocin (IV), ergometrine (IM or IV cautiously), or Ergometrine Maleate/Oxytocin (Syntometrine®) (IM). Oxytocin infusion (Syntocinon®), Carboprost (IM) and Misoprostol® (per rectum) (Arulkumaran *et al.*, 2009). Misoprostol is advocated sublingually in resource poor settings, where other uterotonics may not be available (Vaid *et al.*, 2009) but is not licensed for this indication in the UK and therefore may only be given in accordance with local protocol (NICE, 2007).

Additional less widely used treatments include Tranexamic acid® (IV) which has been identified as potentially effective in arresting bleeding in trauma patients, but requires further validation in PPH (The CRASH-2 Trial Collaborators, 2006). Haematologists may advise and administer other treatments such as recombinant factor VIIa (rFactor VIIa) (NICE, 2007).

Mechanical interventions for the immediate treatment of PPH have been long advocated (Myles, 1985). These include uterine massage, urinary catheterisation and bimanual compression of the uterus. Wide variation in policies for each of these exist across Europe (Winter *et al.,* 2007). Uterine massage is widely advocated. Urinary catheterisation policies exist as an immediate response to PPH in 80% of maternity units in Austria, France, Hungary, Ireland, the Netherlands and the UK, but only 39% of Danish maternity services and 27% of those in Finland. Policies exist regarding implementation of bimanual compression of the uterus to treat PPH in 34-68% of maternity services in EU countries, the exception being the Netherlands (15%) and Italy (21%). Bimanual compression is viewed as effective and easily taught with evidence of knowledge retention in developed and developing countries (Andratta *et al.,* 2011). Consequently bimanual compression of the uterus saves lives. The operator places one hand in the uterus and the other on the fundus, compressing it against the hand in the uterus, as shown in Figure 2.8.

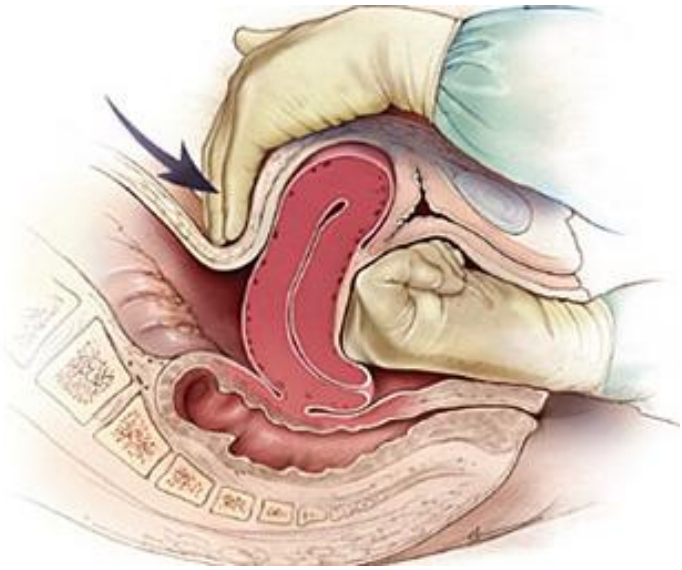


Figure 2.9: Bimanual compression

Surgical treatments include repair of genital tract trauma, compression sutures, brace sutures, balloon tamponade, uterine packing and interventional radiology.

The NICE guidelines concluded there is insufficient evidence to recommend any particular uterotonic or surgical procedure (NICE, 2007).

The United Kingdom Obstetric Surveillance System (UKOSS) studied the management of severe PPH resulting in peripartum haemorrhage, and reported wide variation in treatment strategies, such as brace sutures, rFactor VIIa therapy and intra arterial embolism, prior to these procedures (Knight, 2007; Vais and Bewley, 2006). This provides further evidence of the non-uniform approach to treating PPH and the potentially premature resort to hysterectomy with inherent morbidity. Additionally, a European consortium investigating prevention and immediate management of PPH reported wide variation in practices in 12 member states (Winter *et al*., 2007)

2.2.9 Summary

In summary, what is known includes:

- PPH is common and remains a major cause of mortality and morbidity despite being easily treatable with available resources.
- The incidence appears to be rising.
- The 'true" incidence remains unknown, due to inconsistences in data collection, coding and definition variation.
- Severe maternal morbidity reports are useful adjuncts to mortality reports to identify and reduce substandard care in countries where maternal deaths are rare.
- There are many strategies available and widely utilised to treat PPH, although the effectiveness of these is variably reported.

- PPH has a major impact on women and their families.

Despite being the focus of many studies and reports, uncertainty and gaps in knowledge exist. These include:

- Why, with the availability of multiple resources to treat PPH does it remain a major cause of maternal morbidity and mortality?
- Why have there been several reports of increased incidence of PPH?
- Are existing known risk factors relevant to a contemporaneous population?
- Are novel risk factors responsible for the increasing rates of PPH?
- Would incidence be more accurately recorded and both exemplars in practice and substandard care be identified and addressed with the introduction of an audit system, as apparent in Scotland?
- Despite longstanding and more recently discovered medical, surgical and radiological techniques, which are all readily available, why is PPH, increasing in resource rich countries?

PPH is preventable and treatable, but unlike some other medical emergencies, such as cardiac arrest, management tends to be variable and success difficult to assess. A situation further compounded by the varying definitions, policies and practices employed regionally, nationally and globally. Risk factors for PPH have been identified and yet it remains unpredictable and common even in resource rich countries. The impact on women and their families is considerable, and not entirely understood. Additionally there are financial and resource implications for the NHS, which given the increasing reported incidence, are not inconsiderable, and need addressing urgently. This rise is despite the implementation of risk management strategies and CNST training requirements leading to mandatory updates for staff.

The true picture in England and Wales is unclear, as there is no national or regional reporting mechanism. UKOSS only collects data on rare events due to its methodology and resources available. Thus it can only examine most serious morbidities, which are by definition rare in the UK. The Scottish Confidential Audit into Maternal Morbidity has reported year on year increases in the incidence of PPH, with a corresponding year on year reduction in substandard care, despite the absence of any additional training programmes (Lennox and Marr, 2010). This confirms the value of audit at identifying both good and bad practice in order to promote better care and rectify substandard care. In addition the use of PPH as a key indicator for monitoring substandard care is confirmed (Bouvier-Colle *et al.,* 2001).

2.2.10 Research question

The overarching research goal of this study is to contribute to the improvement in the prediction, prevention, identification and treatment of PPH. The research approach included mixed methodology, focused on gaining insight into this complex clinical problem through quantitative analysis of blood loss and management of the situation in an inner London teaching hospital and a suburban district general hospital in England.

The research question addressed in this thesis is: What is the incidence of PPH in a contemporaneous UK population, is there any improvement in blood loss assessment, and can statistical modelling be employed to predict blood loss at different thresholds?

2.2.10.1 Aims and objectives of this research

Aim: to inform the evidence base to improve the prediction and prevention of PPH.

Objectives employed to achieve this:

Objectives:

1. Devise an effective data collection system to facilitate contemporaneous data retrieval which will not incur additional work for clinical staff
2. To ascertain the current incidence of blood loss, at various levels, in 2 maternity care service providers in England.
3. To compare current PPH rates with historical data for the same maternity services.
4. To identify the contemporaneous risk factors for PPH ≥500ml
5. To identify contemporaneous risk factors for progression to PPH ≥1000 ml and ≥1500 ml).

A methodology was developed to address these omissions in the literature, in an attempt to quantify the incidence of PPH and identify risk factors in a contemporaneous population. This methodology and the rationale for component parts are described in Chapter 3.

Chapter 3: Methodology

3.1 Introduction

The need for high quality evidence to inform policy makers, health care providers, clinicians and users is undisputed (Tunis *et al*., 2003)

Research is a systematic and rigorous investigative process that describes phenomena as well as developing and testing concepts and theories, with the ultimate ambition of adding to scientific knowledge (Bowling, 2009).

In any health related investigation the ultimate aim of research is to improve health outcomes and health care provision. Employing the most appropriate research methodology is integral to ensuring rigour in the work undertaken (Cresswell, 2002).

Whilst randomised controlled trials (RCTs) are often considered the 'gold standard' research methodology, they are not appropriate for all investigations. RCTs reliably determine treatment effects when the design and conduct of the trial minimise potential sources of bias (internal validity), whilst being appropriate and relevant for a defined group of patients and therefore generalisable (external validity) (Rothwell, 2005).

Whilst a treatment effect is commonly investigated in a controlled trial, some research questions are better addressed using alternative methodologies. For

example, when there is no intervention, and the researcher observes the prevalence, incidence, cause or prognosis, or undertakes a cross-sectional, case control or cohort study, often collectively referred to as "observational studies", (Mann, 2003).

Cross-sectional studies determine the number of cases in a population at one point in time (Bowling, 2009). They are effective at determining prevalence for single or multiple outcomes. Due to the single time point for data collection, they are quicker to complete than other research methodologies, and therefore incur less cost. However, they do not differentiate between cause and effect, although they can be used to infer causation and generate future hypotheses for testing. A drawback is that this type of study often uses questionnaires for data collection and this can lead to low response rates and bias caused by differences in responders and non-responders (Mann, 2003).

Case-control studies tend to be retrospective, in that participants with the condition of interest are selected and matched to those who do not (control group). Case control studies determine the significance of predictor variables in relation to a condition, but due to their retrospective nature cannot be used to calculate risk, however, they can generate odds ratio (OR) which usually approximate relative risk (Bowling, 2009). Case control studies are particularly useful when there is a time delay from exposure and disease development and when investigating rare conditions, as they generate lots of information on a limited number of subjects. However, case control studies are subject to sampling and recall bias in addition to issues around confounding variables (Bowling, 2009; Mann, 2003).

Cohort studies are used to determine the incidence of a condition, either prospectively or retrospectively, in a particular population and one cohort can be compared with another (Hackshaw, 2009). Cohort studies are often undertaken when an RCT would be unethical, for example, withholding uterotonic medication for the third stage of labour, irrespective of risk of PPH. Cohort studies identify potential causes prior to the outcome occurring and the effect of each variable on developing the outcome can be calculated. Loss to follow up can be problematic in prospective cohort studies, if they are conducted over many years, which can affect results and inferences, especially when investigating rare conditions.

Retrospective cohort studies have the advantage that the data are collected for another purpose and therefore this study design minimises bias but the trade off is that clinical practice may have already changed compared to the time when the cohort study was conducted. Other disadvantages of this study design include the data quality of the variables and outcome of interest may be less rigorously collected because the cohort was formed for another purpose (Mann, 2003), and the inability to control for confounding variables (Bowling, 2009).

Secondary data analyses using pre-exiting databases have the advantage of being convenient and enable the inclusion of large numbers of people with data entered prospectively and retrospectively. Thus facilitating a) the identification of people with and without certain conditions or outcomes for a case controlled study, b) a sample for cross sectional investigation and c) the construction of a cohort. This methodology commonly employs routinely collected data, which has the disadvantage of potential data entry errors and omissions, but the advantage of diminished bias as it is collected independently of specific hypotheses (Cresswell, 2002).

3.2 Philosophical framework for research

Each branch of scientific enquiry is rooted in theoretical perspectives, known as paradigms. These are important because these overarching philosophical or ideological standpoints form a framework for generating and interpreting knowledge. Paradigms consist of a set of assumptions, or way of viewing the world, and it from these perspectives that research questions are formulated (Bowling, 2009). Research is not value-free, therefore it is important for researchers to identify and acknowledge personal theoretical perspectives and reflect and report these when designing studies and analysing data.

The overarching philosophical or ideological framework and the investigators assumptions about the nature of knowledge or epistemiological standpoint inform the design and method of investigation used. For example, the interpretivist paradigm maintains that knowledge is socially constructed and therefore reality is subjective. In health care research this paradigm underpins qualitative research methodologies. Conversely a positivist paradigm maintains that reality is established and knowledge can be produced through rigorous quantitative methodologies. Positivism assumes a single objective reality, ascertainable by the senses, and able to be tested in accordance with laws of scientific method (Bowling, 2009). In reality, this is often an artificial dichotomy with many research designs using mixed methods to provide complementary components of a research project.

Investigators can undertake research from two perspectives. They can begin with general ideas from which theories and hypotheses are developed, which are then tested by collecting and analysing data, this is known as deductive reasoning. Conversely the researcher can start with observations from which they

accumulate and develop general statements and hypotheses that are tested, this is inductive reasoning (May, 1993).

In the current study, the positivist paradigm with deductive reasoning was used. This was the appropriate philosophical paradigm because the aim of the study was to identify and investigate causal relationships between risk factors and postpartum blood loss. The starting point was the observed increase in PPH, seen both anecdotally in the participating units and reported in the literature (Wen *et al*., 2005; Ford *et al*., 2009; Knight *et al*., 2009). The general ideas from which the hypothesis was developed were based on the notion that better prediction of PPH can contribute to improved outcomes. Data were then collected and analysed using multilevel modelling to ascertain which independent risk factors were associated with estimated blood loss, at different levels and adjust for confounding factors.

Whilst acknowledging the potential for bias in all research methodologies, most readily addressed by randomised controlled trials, in the current study this was addressed in several wys. 1) the weighted sampling strategy described in Section 3.4, 2) minimising the number of staff members reviewing case notes and entering data, and ensuring ongoing inter-user comparison, 3) independent review in 10% of all cases, as described in the Chapter 3 (Methods).

3.3 Ethical framework for research

All research within the NHS must conform to an ethical framework to ensure the wellbeing of participants and researchers as well as ensuring high quality data are obtained. The origins of this framework date back to the Nuremberg Trials (1947) which exposed the medical experiments carried out by doctors in Nazi Germany on concentration camp victims. Following this the Nuremberg Code of ethics

emerged outlining the 'standards to which physicians must conform when carrying out experiments on human subjects'. A draft code of ethics on human experimentation was first published in the BMJ on 27th October 1962 (BMJ, 1962).

A revised version was developed and accepted at a meeting of the World Medical Association in Helsinki, together with the edict that this would be known as the 'Declaration of Helsinki' (BMJ, 1964). Although its' roots were firmly in the Nuremberg Code, the initial Helsinki agreement changed 'the consent of the human subject is absolutely essential' to include provision for a 'legal guardian' to give consent in cases of 'legal incapacity'. The other omission was the statement 'during the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible'. Which was replaced with 'the investigator or investigating team should discontinue the research if in his or their judgement it may, if continued, be harmful to the individual'. The first revision (1975) was extensive and introduced the requirement of independent committees to review protocols to ensure the conduct of medical research, in addition to significant elaboration around the requirements for informed consent (Flanigan, 1997). Nothing was removed from the earlier version and considerable information was added, additionally the sexist language utilized in the 1964 version was updated, for example the phrase 'fully qualified medical man' was changed to 'medically qualified person'.

Further minimal revisions took place in Venice in 1983 and Hong Kong in 1989. In South Africa, 1996 whilst the text changed little there was, for the first time, specific reference to placebos, and is fundamental to the USA Food and Drug Administrations referral to the 1989 version in its regulations (Temple, 2003). In

Edinburgh, 2000 the document was restructured. Prior to this version the Declaration dichotomised research into therapeutic (potentially benefitting the subject) and non-therapeutic (no direct benefit to the subject) the new category of 'Medical Research Combined with Medical Care' was introduced as a subset of 'all medical research involving human subjects'. 'Non-therapeutic' research considered synonymous with 'healthy volunteers' was removed as a distinct category, and an explicit statement permitting participation of healthy volunteers included. This more logical categorisation has been advocated as removing previous ambiguity (Levine, 2000).

3.3.1 Regulatory Approvals

MHRA approval

MHRA approval was not required for the current observational study as there was no investigative medicinal (IMP) product being tested.

Ethics approval

In the current study because information was obtained from NHS databases and other data sources ethical approval from the National Research Ethics Committee was required.

Whilst no single framework exists to ensure ethical research (Soobrayan *et al*., 2003) there are key ethical theories that are integral to all aspects of it. The mechanisms employed to regulate research practices are derived from utilitarian and deontological theories. They query what should be done to achieve the greatest good and to maintain obligations inherent in human interaction. Utilitarian theories are concerned with purposes and consequences ("teleologocal"

or "consequentialist" theories). Deontalogical theories can be further subdivided into those based on "duties" and those based on "rights" (Kimmel, 1998).

Subdivisions of theory are common, Miles and Huberman (1994) identify seven potential frameworks but explain four- utilitarian, deontological, relational and ecological, each of which bring differing priorities to each part of the research process. For example utilitarianism prioritises informed consent, the deontological – reciprocity, the relational collaboration and the ecological prioritising cultural sensitivity (Miles and Huberman, 1994). The evolution of ethical theory within the operationalised principles employed today is hard to trace. Recently research into informed consent has demonstrated its complexity (Sin, 2005; Wiles *et al*., 2005). Others have identified further difficulties with the concept of informed consent especially pertaining to health, when research designs are too complex for a person normally considered to have capacity to give consent, to fully comprehend the consequences (O'Neill, 2006).

The first Research Ethics Committee (REC) was established in the UK in 1966. The primary function of RECs is to save guard and protect patients and the general public from harm caused by unethical research but also to encourage and promote research that improves health and healthcare (Alberti, 2000). In addition to reviewing clinical trials, the REC reviews other research protocols for both clinical and social researchers in Health, as approval is required in the majority of cases prior to research being undertaken involving NHS patients, staff or premises. Some exceptions to this rule exist and the Health Research Authority has a web based tool to ascertain whether a study requires full approval (www.hra-decisiontools.org.uk). In accordance with the EU Directive and Clinical

Trials Regulations a REC must given an opinion within 60 days of receipt of a valid application.

Research and Development (R and D) approval

In addition to REC approval all research projects on NHS premises, or with NHS patients or staff need to be reviewed and approved by the Research and Development department in each participating centre. NHS England states that research and research evidence is integral to the day to day business of the NHS. The Department of Health invests in research to support government objectives for public health, health services and social care, in addition to contributing to the government science strategy, within the NHS, R and D ensures:

1) Policies for health, health care and social care are based on reliable evidence of need and of what works best to meet those needs.
2) Improved interventions are developed to promote health, treat ill health and provide social care.
3) Information is available to those responsible for health and social care services on what works and does not, and on proven ways of improving quality, access and efficiency.

Best Research for Best Health (DoH, 2006) outlined a 5 year Research and Development Strategy for NHS England, which included the establishment of phased funding that ensured by 2009 all Research and Development (R and D) would be funded through the National Institute for Health Research (NIHR). R and D Committees in each Trust have overall responsibility for the strategic direction, decision-making and alignment of research themes with local, regional and national priorities.

R and D Directors have executive responsibility for the R and D functions, chairing R and D committees and reporting R and D output to the Trust Board.

The management of R and D within the Trusts is the responsibility of the R and D Directors, Assistant Director and the R and D office. R and D offices are responsible for ensuring the core functions of R and D are fulfilled, ensuring that all research is of high quality, ethically sound and of benefit to the patient. Functions of the R and D office include:

- The collection and collation of essential information about all research within the Trust that involves Trust patients or uses Trust resources directly or indirectly.
- Registers all projects on the R and D database.
- Costs registered projects.
- Administers Clinical Projects Peer Review Groups.
- Ensure research governance procedures are undertaken.

A high priority for R and D offices is to ensure researchers and potential researchers comprehend the research process when commencing a project. To facilitate this many departments offer support and advice at various stages, including protocol development and peer review, identification of potential funding opportunities, advice regarding ethical review submission, budgeting for the project and ongoing advice and support to enable the researcher to undertake quality research.

3.4 Sampling strategy

The design for the study presented in this thesis was carefully considered prior to initiation. The benefit of extracting a large volume of contemporaneous data from NHS electronic patient records had to be counterbalanced with the widely acknowledged error rates inherent in clinical data. The ideal would have been to

check all the electronic data against the handheld notes and other medical records for accuracy. However, for a study with data from more than 10,000 women and over 12 month period, this was not feasible due to resource constraints. Consequentially another strategy was required for ensuring data accuracy.

Looking at a range of approaches to deal with this it was apparent that many fields of biological and medical research, when the population of interest is large, employ a sampling strategy. There are several approaches that could be used but all are based on statistical probability which has its roots in the investigation of patterns from gaming tables using dice and cards, this theory of statistics underpins medical statistics as it is extrapolated to a sample of the community, or group of patients with a disease, to represent the population, all people in one area or all patients with a certain disease (Peacock and Peacock, 2011).

Random sampling gives everyone in the target population an equal, and non-zero, chance of selection. Unrestricted random sampling means members of the population are numbered and some of them are selected using random numbers. Those selected are then replaced in the population prior to the next selection. Whilst each population member has an equal chance of selection, it is possible that each unit/person could be selected more than once.

Simple random sampling refers to members of the population being numbered and selected as above, but those selected are not replaced in the population, thus all members of the population have an equal chance of selection and can only be selected once. This method of sampling without replacement undermines the

underlying statistical assumption of independence of the sample and therefore a correction adjustment to the formula would be required (Blalock, 1972). Both these techniques would be unsuitable for the current study because the sample could fail to be representative of blood loss at all levels, as the random sampling could mean over or under representation at all or any level.

Truly random sampling is rare as often lists are organised in alphabetical order, for example, therefore systematic random sampling is achieved. This fails to give the whole population an equal chance of inclusion, rather, the chance of selection is dependent on the previous unit/person selected (Bowling, 2009). A random sample will be representative of the population from which it is drawn because the characteristics of individuals are not considered when selection is made (Peacock and Peacock, 2013). As with random sampling this technique would not be useful in the current study, as it may not provide information regarding all levels of blood loss.

A stratified sample is used when fixed numbers are required from particular sections of the population in order to balance across the sample. This method of sampling provides the best overall estimate where it is weighted in accordance with the incidence of each stratum (Pocock and Pocock, 2011). Disproportionate or weighted sampling is an extension of this, Adoption of a pre-specified sampling frame would enable contemporaneous selection of a random sample stratified according to blood loss at all levels but focusing on those of greatest interest i.e., the largest volumes.

Quota sampling is where the numbers selected for the sample are proportionate to the incidence in the population being investigated, for example people in a certain age range. This sampling is commonly used in market research. It has the disadvantage that those included may differ from those not selected (Peacock and Peacock, 2011). This would not be appropriate for the current study as the majority of women would have lower levels of blood loss and therefore the sample would provide more information about lesser blood loss.

Cluster sampling involves selected those who naturally fall into groups, however this sampling strategy is less precise than random sampling and therefore corrections need to be made later in the analyses (the standard error is likely to be higher) (Bowling, 2009). Similarly in the current study sampling could have been undertaken according to blood loss categories, but the proportions according to these and the inherent imprecision would render this strategy less than ideal.

3.5 Analyses

The specific approaches for data analysis in my study are further described in detail in Chapter 4 methods.

Initially data were summarised to facilitate data monitoring and cleaning to ensure the accuracy of recorded data. Descriptive statistics were used to provide information about the sample, facilitating identification of the group and comparison with the general population from which it was drawn, but also to assess generalisability with other communities (Peacock and Peacock, 2011).

Additionally these basic statistics provided the foundation upon which further analytical processes could be produced.

Continuous variables, such as blood loss and birthweight, were classified in groups to ease handling and reporting, for example: PPH > 500 ml; 500-999 ml; 1000-1499 ml; ≥ 1500 ml. This avoids the problems of excluded data and loss of statistical power caused by dichotomizing data, that is putting all data into 2 categories. Placing, for example, PPH or no PPH, or birthweight <4 kg or ≥ 4kg.

Continuous data were summarised using means (simple average of all data), most commonly the arithmetic mean, when the data distribution was reasonably symmetrical. But when the distribution of the data was non-normal, most commonly with a positive skew (that is the tail on the right side of the distribution curve is longer) geometric mean was calculated. This involves replacing each value with the logarithm of its base, and using this to calculate the arithmetic mean. This is then back transformed, producing a mean that is in the same units as the original data (Peacock and Peacock, 2011).

For all means, standard deviations were calculated, indicating the dispersion of the data that is the average difference between the mean and each data point. This was used in preference to the variance because standard deviation is in the same units as the mean, and is easier to interpret (Peacock and Peacock, 2011)

Interquartile ranges were calculated for certain data points, for example the Index of Multiple Deprivation (IMD), which are commonly reported in this way. The interquartile range includes the middle 50% of values and is bounded by the

upper and lower quartiles. The data are ranked, as for calculating the median, and the lower quartile includes those values below the point at which 25% of the data sit. The upper quartile is similarly calculated as the data above the top 25% (Peacock and Peacock, 2011).

As in any medical statistics in my study it was important to ascertain the independence of variables. Incorrect assignment of independence leads to wrong conclusions. Peacock and Peacock (2011) state the "theory of statistics" underpins medical statistics but the theory of probability facilitates investigation. Probability is the number of times an event occurs, which is estimated from a proportion calculated in a sample (Peacock and Peacock, 2011). Probability always lies between 0 and 1. With 0 being a never event and 1 meaning it always occurs.

There are several versions of data distribution, for example Binomial and Poisson, which are appropriate when using discrete variables within limited sets of values, but given the nature of PPH, and number of variables used in the current study, would be inappropriate. Continuous probability variables were used because these distributions use any values within given limits. In this situation probabilities are determined by the area under the curve between two values. The most common form of continuous probability is Normal distribution, with its' characteristic bell shaped curve. Variations in Normal distribution are manifold, depending on individual mean and standard variations, but these can be converted into a standard format, which has mean=0 and standard deviation =1 (Coggan, 2009). As a sample size increases the sampling distribution of any estimated quantity is Normal in accordance with the central limit theorem (Peacock and Peacock, 2011)

and therefore, given the size of the current project Normal distribution was achieved.

When undertaking statistical analyses there is always uncertainty and various statistical tests can be undertaken to identify and account for these. The mean of multiple samples produce the sampling distribution of the mean and the precision of the sample mean can be estimated by calculating the standard deviation from the mean (Bland, 2000).

I chose to calculate confidence intervals (CI) to quantify the certainty of findings. Although other percentages could have been used, most commonly 95% CI are recommended when the sample size is large (>100). Therefore, in common with most other studies, a 95% CI was the margin of error around the estimate indicating the precision of that estimate (Peacock and Peacock, 2011; Coggan, 2009).

Another form of expressing probability is the P value, which is expressed as a value between 0 and 1. It is derived from a statistical test and expresses the weight of evidence for or against the stated null hypothesis (Bland, 2000) with the cut off for statistical significance commonly 0.05 (5%). However p values are less informative than 95% confidence intervals and are given as an addition rather than the main route to determine how important study results are.

Univariate analysis, looking at the impact of each single variable on the outcome variable, for example body mass index (BMI) on PPH, would initially be

undertaken to refute or identify variables associated with the outcome variable of interest.

Due to the large number of variables being assessed some would advocate the use of a statistical correction for multiple comparisons, such as Bonferroni (Peacock and Peacock, 2011). However others have suggested use of such adjustment is not appropriate in epidemiological studies and clinical trials as this leads to over adjustment because of the assumption that all null hypotheses are simultaneously true, which is rarely the case. Additionally using such an adjustment involves undertaking numerous tests, therefore interpretation of the findings can be influenced by the number of tests performed, increasing the likelihood of a type II statistical error (where important differences are rendered non-significant) (Perneger, 1998). Following statistical consultation it was decided not to make such an adjustment in the current study because of the multiple comparisons required.

Multiple regression analysis would be undertaken, should the associations seen in simple linear regression reveal inconsistent results. This was anticipated in light of widely published evidence in the literature.

3.6 Clinical Study Regulations in Europe

3.6.1 EU Directive and GCP

When planning my study the myriad of regulation relating to clinical studies were considered and appropriate approvals obtained, specific details are described in Chapter 4. The complexity of regulatory framework for human research is detailed below.

In May 2004 The European Clinical Trial Directive 2001/20/EC for clinical trials was adopted across EU Member States (Directive 2001/20/EC, 2001). These regulations relate to the implementation of Good Clinical Practice (GCP), in the conduct of clinical trials of investigational medicinal products (IMPs). GCP was developed by the regulatory authorities in Europe, USA and Japan at the International Conference of Harmonisation in 1997, but was not embedded in law until The Medicines for Human Use (Clinical Trials) Regulations 2004 (Medicines for Human Use (Clinical Trials) Regulations, 2004). The main principle of GCP is that 'the rights, safety and wellbeing of trial participants are of paramount importance and should prevail over the interests of society'. Anyone designing or conducting a clinical trial employing an IMP must comply with these regulations.

The Medicines and Healthcare Regulatory Agency (MHRA) provide guidance as to what constitutes an IMP (MHRA, 2007). Whilst investigations not involving an IMP are exempt from these regulations, the expectations of stakeholders is that all trials will be conducted to the same robust standard, thus ensuring patient safety and scientific credibility in all trials (Bollapragarda *et al*., 2007). All personnel involved with clinical research therefore need to be trained in GCP, in addition to being relevantly qualified (UKCRN, 2007).

3.6.2 Data Protection Act (1998)

The UK Data Protection Act 1998 exists to protect the privacy and confidentiality of individuals, including those accessing health and social care and the principles are shown in Table 3.1.

Table 3.1: Principles of the Data protection Act, 1998

1. Personal data shall be processed fairly and lawfully.
2. Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes.
3. Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed.
4. Personal data shall be accurate and, where necessary, kept up to date.
5. Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes.
6. Personal data shall be processed in accordance with the rights of data subjects under this Act.
7. Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data.
8. Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data.

It is the law around obtaining, storing and anonymising personal data, but has caused confusion in its' interpretation and implementation (Metcalfe *et al*., 2008). The Data Protection Act defines and limits patient identifiable data (Data Protection Act, 1998). Patient identifiable data is defined as all personal information from which a person can be directly or indirectly identified, for example name and postcode. It also includes encrypted data, if the solution for decryption remains in use, for example hospital or NHS number. Whilst many authorities recommend informed consent is obtained for all participants, whether it involves direct contact or access to medical records, this is not an obligation under the law and the Data Protection Act envisages circumstances when personal health records may be accessed and used in medical research without consent or complete anonymisation (Falconer, 2000). It has been suggested that

NHS data controllers have been over-zealous in their interpretation of the Data Protection Act, namely ignoring Section 33, which permits the further processing of previously collected personal data for research purposes (Data Protection Act 1998; Iveson *et al*., 2006; Walley, 2006). Further confusion has arisen due to misinterpretation of the common law of confidentiality, established in case law, and therefore is open to interpretation, states that patient identifiable data should not be disclosed to third parties, regardless of compliance with the Data Protection Act. This contradicts section 60 of the Health and Social Care Act 2001, which states that collection of patient identifiable data without patient consent is lawful, despite the duty of confidentiality (Department of Health, 2003). Additionally the Human Rights Act 1998 assumes compliance with the Data Protection Act and the common law duty of confidentiality, in Article 8 (1) it states 'Everyone has the right to respect for his private and family life, his home and his correspondence' and that 'the protection of personal data, not least medical data, is of fundamental importance to a person's enjoyment of his or her right to respect for private and family life' (Z v Finland, 1998, cited by Haynes *et al*., 2007)

3.6.3 Caldicott Guardianship

Although informed consent was not required for the aspect of the STOP study covered in my thesis, confidentiality had to be ensured, as it is integral to the relationship between patients, healthcare providers and researchers. In 1997 the Chief Medical Officer for England, in response to concerns about patient confidentiality in light of widespread information technology, commissioned a review of data handling and the development of principles to underpin the approach of NHS Organisations when protecting and using patient identifiable

data. This Committee, chaired by Dame Fiona Caldicott, cited six principles (Gill, 1997):

1. Justify the purposes) for using patient identifiable information
2. Only use patient identifiable information when absolutely necessary
3. Use the minimum identifiable data required
4. Access to patient identifiable data should be on a strict need-to-know basis.
5. Everyone must understand their responsibilities regarding patient identifiable information
6. Understand and comply with the law regarding patient identifiable information.

In the current study all data collected had minimal identifiers, achieved with a link-anonymised system that generated a unique study identification number (ID) this ensured compliance with the Caldicott principles and good clinical practice (GCP). Demographic information, date of birth and maternal initials, were collected to enable the researcher to identify all medical records and facilitate communication with participants (for the qualitative aspect of the larger STOP study). These data were stored separately from clinical data.

3.6.4.Electronic data collection and ECRIN guidance

Since my study was extracting electronic patient records from NHS systems and storing information on an Internet database it was important to review the literature and guidance surrounding the use of electronic data capture and storage. Electronic data collection (EDC) has been advocated as effective for

recording research and clinical data, and its introduction and evolution has been expedited by technological developments in recent years.

EDC was first introduced in clinical trials in the 1970s, when the Institute for Biological Research and Development (IBRD) provided study specific computers for direct data entry by members of a clinical collaboration onto the IBRD mainframe. Data were cleaned and reports provided for Abbott Pharmaceuticals. These early systems used "thick-client" software, necessitating a modem and periodic transmission of information through analogue telephone lines, which was slow and the delay between data receipt and query generation apparent. Study specific computers were installed in clinical areas, coupled with cumbersome programming and slow speed machines initial trials employing these methods were unpopular with clinicians (Handelsman, 2010).

In the 1990s accessibility of the internet, combined with the development of high speed machines and secure servers meant that EDC became a reliable form of gathering contemporaneous accurate information, with many web-based software solutions available, both in customised and "off the shelf" formats.

Electronic patient records have been widely introduced in all aspects of clinical health provision (Bewley et al, 2010; Mutic et al, 2010; Raynor, 2010) and have been cited as improving care (Scopelliti, 2010). The introduction of electronic patient records is widely advocated (Protti, 2007) with slow progress attributed to political and contractual issues (Robertson et al, 2010).

Whilst the term 'electronic data management system' has been broadly used to describe a variety of systems, from stand alone data entry ports to complex programmes underpinning international multicentre studies, these have long been advocated for clinical trials (Litchfield *et al*., 2005; Kush *et al*., 2003; Kiuchi and Kaihara, 1997; McFadden *et al.*, 1995).

Combining clinical and research records within compatible electronic databases could further improve the overall quality of data and care. Organisations such as the Clinical Data Interchange Standards Consortium (CDISC) and Health Level Seven (HL7) exist to ensure quality whilst pursuing interoperability of such systems (de Montjoie, 2009; HL7 International, 2010).

The proportion of trials fully utilising EDC is unclear. A survey of practice regarding data management for 947 Canadian studies (2006- 2007) concluded that 41% relied on internet data collection, and these were more likely to be industry rather than academically funded studies. Overall the sophistication of the systems used was similar regardless of funding source, but the sample size tended to be larger in the industry funded studies (El Emam *et al.*, 2009).

The European Clinical Research Infrastructure Network (ECRIN) established in 2004 to connect academic clinical research throughout Europe. Whilst identifying fundamental differences and discrepancies between regions, their 2007 survey found that of those trials using EDC systems 48% were commercially available and 38% employed proprietary systems. Additionally some centres used open source solutions, for example "Open Clinica", but these tended to be small studies (ECRIN, 2007). ECRIN have also devised a list of requirements to ensure data management meets GCP standards, these are shown in Table 3.2.

Table 3.2: ECRIN requirements for GCP compliance with regard to EDC

	Summary EDC requirements for GCP
1	Software must be validated
2	Restricted access
3	Audit trail to data
4	Traceability- changes to data recorded
5	Written instructions for GCP compliance
6	Check of data quality
7	Encryption of ID
8	Automatic back up of data
9	Blinding of subject

In the US the Food and Drug Administration (FDA) issued regulations regarding electronic signatures and records in 1997 (21 CFR 11) followed in 1999 by further regulations regarding computerised systems to create, modify, maintain, archive retrieve or transmit clinical data (Department of Health and Human Services, 1997; FDA, 1999). The aim of these regulations was to ensure the integrity of data from computerized systems. Further guidance regarding electronic signatures and software validations were issued in 2001 and 2002 (Food and Drug (FDA, 2001; FDA, 2002).

Traditional methods of data collection have been associated with delays in data review and transcription errors (Mitchel *et al*., 2003). The Maternal and Fetal Research Unit have employed electronic data management for several single and multicentre clinical trials (Poston *et al*., 2006; Baker *et al*., 2009) and have a partnership with a commercial company who specialise in developing web based solutions for clinical trials and registers (MedSciNet[AB]). Discussions with their

representative and the Information Technologists for participating Trusts importation form NHS databases onto a secure Internet platform appeared technically possible. Confirmation that the MedSciNet[AB] system adhered to FDA regulations as well as the Data Protection Act, Caldicott Guardianship and ECRIN recommendations reassured the regulatory bodies regarding data security.

3.7 Authorisations

3.7.1 The Protocol

This is a document containing a full description of the background, aims, objectives and methods of a clinical trial, including dissemination of findings. The protocol is an essential document for Research and Ethics Committee (REC) and local Research and Development (R and D) approval prior to starting the study. Regulations dictate that adherence to the protocol is mandatory when undertaking a clinical trial, this is especially the case when undertaking an interventional study, but GCP dictates adherence to a protocol is the accepted standard for clinical research. Therefore in the current study the protocol was developed and all study processes were followed. The STOP study protocol, which includes the work presented in this thesis is shown in Appendix 1. Variations to the protocol need to be notified to the sponsor, the MHRA (in trials using an IMP) the REC and R and D department at all participating sites.

3.7.2 The Sponsor

The Sponsor is defined as an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial (Clinical trials tool kit, 2007). In an industry funded study the

Sponsor is invariably a drug company, but for studies funded by public bodies or charities often the employer of the Chief Investigator will be the Sponsor. Since the EU Directive 2004 it has been illegal to commence as study without identifying a Sponsor.

3.8 Summary

Despite randomised controlled trials being advocated as the "gold standard" for clinical research, due to its capacity to compare an intervention with no intervention, or placebo with random allocation and controlling for confounding variables, it would not be appropriate for the current investigation. It would not be ethical to assign women to no treatment, given the evidence of reported effectiveness of active management of the third stage of labour.
Additionally the aim of the current study was to ascertain the incidence of PPH in a contemporaneous population and to develop prediction models to identify those at risk of PPH at various levels. It was therefore appropriate to use an observational methodology.

A cross sectional study would inform us of incidence at a single time point, but a more comprehensive view was required, therefore identifying incidence over the course of a year was deemed advantageous, which would take into account seasonal fluctuations. A case control study was considered but whilst providing information regarding the cases of greatest interest (largest blood loss), it would limit information about lesser levels of blood loss.

A cohort study was therefore the methodology of choice as it would provide information about the whole cohort, and comparison with the earlier cohort would be possible. However given the anticipated size of the cohort (around 9500 women) resources were insufficient for scrutiny of all medical records to be undertaken. The weighted sampling strategy, whilst novel in medical research, is commonly used in epidemiology and accountancy would enable scrutiny of a realistic and manageable sample within the available resources of the project and enable observations and investigation of all levels of blood loss.

Electronic data management facilitated importation of summary data from NHS databases without being burdensome for clinical staff, and with the reassurances of a secure system would facilitate data entry being accessible on both sites and all geographical areas. Previous experience with electronic data management further confirmed this as desirable for the current study.

Having outlined the theories and methodologies considered prior to development of the current work. Chapter 4 outlines the methods employed to undertake this work and address the research questions posed.

Chapter 4: Methods

4.1 Introduction

The work included in this PhD thesis was undertaken in tandem and as part of the Surveillance and Treatment Of Postpartum haemorrhage (STOP) study.

4.2 The STOP study

The STOP study was funded by the Guys and St Thomas' Charity (registered charity 251983; Chief Investigator (CI) Susan Bewley; Co-Investigators Annette Briley, Jane Sandall and Mark Waterstone). The main goal of the study was to ascertain whether the prediction, prevention, identification and treatment of postpartum haemorrhage could be improved.

4.2.1. My role in the STOP study

I was the STOP study manager and co-ordinator. I was jointly responsible for developing the idea, preparing and submitting the funding application, developing the protocol, patient information sheets and consent forms (for the qualitative aspect of the study), obtaining regulatory approvals, database development, random case generation, review of the notes, discussion and decisions regarding ambiguous cases, facilitation of study advisory group, undertaking qualitative interviews with women, their birth partners and the staff involved in the emergency and analyses of all data. Additional support for recruitment, and data collection and entry was provided as part of the main study by Mrs Henrietta Ballard (research midwife).

Mr Paul Seed, study statistician, provided support and supervision for the main study analysis and for this thesis. A formal Trial Steering Committee was not required as STOP was an observational study, however a Study Advisory Group was formed to provide advice and support during the initial set up and throughout the duration of the study.

The specific objectives of this PhD in relation to the STOP study are outlined in Table 4.1. The main study design is described below, followed by the methodology for the specific objectives undertaken as part of this PhD, which focuses on the prediction of PPH at various thresholds.

Table 4.1: Objectives and activities for the main STOP study and those undertaken within this PhD.

	STOP study Objectives/activities	**PhD Objectives/activities**
1	Investigate current guidelines regarding the management of PPH in different units.	
2.	Devise a data collection system that facilitates contemporaneous data retrieval but is not onerous for clinical staff.	√
3.	1) Investigate the professional, personal and team factors that influence the management of haemorrhage. 2) Ascertain and examine multidisciplinary staff attitudes to the management of this complication. 3) Explore the experience of haemorrhage from the sufferer's perspective. This will include their views of the professionals' response to the emergency and the impact on them and their families.	
5.	Ascertain the current incidence of PPH at various levels of blood loss in 2 maternity service providers.	√
6.	Identify contemporaneous risk factors for PPH and in 2 units	√
7.	Identify risk factors for progression to moderate and severe PPH in 2 units	√
8.	Compare trends in PPH over time in 2 maternity services providers in addition to comparing PPH rates in these two Centres with a contemporaneous data set	√
9	To compare the evidence of actions taken from maternity records with the protocols in 2 maternity services providers	√
10.	Develop a single unified protocol for the management of PPH in the participating Centres.	
11.	Establish an internet-based data collection system to continuously monitor all haemorrhage and the quality of care in analysis of cases of severe haemorrhage. This will facilitate effective monitoring and auditing in participating units.	
12.	If deemed appropriate establish a support group for women who experience PPH.	

A detailed literature review identifying those at risk of PPH, trends in PPH and the current management and treatment of the condition enabled the establishment of feasible research questions.

For the main STOP study a mixed methods approach was adopted: quantitative methods to achieve the precision, scientific and statistical tools required to answer specific questions regarding risk factors and current practice (Cresswell, 2009); qualitative methodologies were used to facilitate in-depth exploration of the experience of PPH for women, their birth partners and the health care professionals involved in this common emergency. It was anticipated that these data would focus on the management of the PPH and therefore this aspect of the STOP study was excluded form the PhD thesis that concentrated on predication.

This approach enabled the STOP study to provide a complete, contemporaneous account of PPH events including identification of the incidence, current risk factors for PPH and for progression from minor to major haemorrhage, it's management and impact. This triangulation would also confirm the validity of the findings and ultimately improve the rigour of the data (Brannen, 1992).

This thesis, whilst acknowledging the added value of the qualitative methodology, will focus on the quantitative aspects of the work. The interview and management data will be analysed and reported separately. The creation of the database, data collection and univariate and multivariate regression models for the prediction of PPH at different levels were considered a discreet project within STOP, with the potential to contribute to the evidence base and influence practice.

4.2 Site selection

Initially the STOP study was conceived as a single Centre project to investigate the PPH in the unit where the idea was developed (Centre 1). However it became apparent that, an additional Centre was required to increase generalisability. This was considered essential because the initial Centre is a tertiary referral unit serving a high-risk inner city population; consequently PPH rates in that Centre may be unrepresentative of the general population. It is estimated that 30% of UK babies are born in large teaching hospitals (Birthchoice, 2010) (www.birthchoice.co.uk). Therefore a District General Hospital (DGH) would be desirable, both in terms of being where the majority of babies are born, but also potentially because it could provide a more realistic incidence of PPH. Additionally, staff retention and recruitment in inner city units has historically been problematic (RCM, 2008; Davis, 2005) with reports of increased employment longevity in more rural locations (www.rcm.org.uk). It was anticipated that staff experience and knowledge could also impact on the management of PPH and therefore inclusion of a district general hospital provided diversity in this area too.

Pragmatically, involvement of a unit that was easily accessible was desirable. Student midwives training through a different university could provide further educational diversity regarding this common obstetric complication. The second site was additionally selected to enable comparison with a seminal study on severe maternal morbidity, including PPH (Waterstone *et al.*, 2003). The second unit was a DGH 20 miles south of the tertiary referral unit with an annual birth rate of approximately 3000, with similar protocols, and similar service configuration to Centre 1, being a consultant led obstetric unit with an alongside midwife led unit. The project was presented to the Department of Obstetrics and Gynaecology and the Research and Development department at the Centre and they agreed to collaborate with us for this study.

4.3 Population and sample size

The sample size was determined based on the incidence of the primary outcome, PPH, in the two participating Centres. The combined annual birth rate in the year preceding the study was 9,515 (6,540 and 2,975). With rising birth rates in both Centres, it was anticipated that data would be available for around 10,000 women in the index year of 2008/2009. As the study was observational by design, with no single intervention or risk factor whose influence was to be assessed, a conventional power calculation was not undertaken (Rothman, 1990).

Collection of a full 12 months of data (01/08/2008- 31/07/2009) was considered necessary to eliminate possible seasonal fluctuations and population diversity was maximized by inclusion of a tertiary referral Centre and a district general hospital.

4.4 Weighted sampling strategy and selection of notes for review

Since review of all maternity records was not feasible within available resources, a random weighted sample of maternity records was selected to provide a representative sample set for detailed review. The prospective weighting strategy was calculated following discussion with the study statistician using the incidence of blood loss at various levels in a clinical dataset available in Centre 1 for 2000-2005 in conjunction with regional data for PPH >1500ml from the earlier COSMO study (1997-1998) (Waterstone *et al.*, 2003).

The use of a weighted sample design, known as disproportionate stratified sampling, whilst novel in obstetrics, is a method commonly employed in epidemiological and observational studies (Korn and Graubard, 1999) and non-clinical contexts (Malgarini, 2005). Women who had a PPH were selected on the

basis of blood loss category, together with a random selection of unaffected women, to achieve high statistical power. Standard errors were adjusted for the sampling strategy using the Huber-White estimator (Huber, 1967).

This statistical methodology is well established for all types of summary and analysis (Kish, 1965) with suitable software widely available (Kreuter and Valliant, 2007). The main advantage of a weighted sample is similar to that of a case-control design: by selecting all the most interesting subjects and only a representative sample of the controls (as determined by a pre-specified sampling frame), high power is maintained whilst greatly reducing the workload. However, common problems with case-control studies are avoided: data-collection is identical for all subjects, and re-allocation between groups is possible.

Within one week of delivery, one in twelve women were randomly selected from those with imported estimated blood loss recorded on the electronic patient record as 25-499 ml and one in six women with recorded estimated blood loss of 500-999 ml. All available medical records were scrutinised for these women and for all those who had electronically reported estimated blood loss of ≥1000 ml, no electronically documented blood loss or where electronically reported estimated blood loss was <25 ml and for all women for whom blood or blood products were ordered. Random selection was achieved by witnessed and recorded paired dice throws. Testing for any systematic bias towards any particular number validated the process of random selection, using fair dice. The frequencies were 371 (for 1), 372 (for 2), 396 (for 3), 369 (for 4), 383 (for 5), 384 (for 6) for a sample of the first 2275 throws; Chi-sq = 1.432, p = 0.921 (5 degrees of freedom).

4.5 Protocol development

In accordance with Good Clinical Practice (GCP) (MRC, 2004a; MRC, 2004b; NIHR, 2004) a protocol for the STOP study was developed by the investigators (Annette Briley, Susan Bewley, Mark Waterstone and Jane Sandall) and further refined in collaboration with the STOP Study Advisory Group, the aspects of the protocol to be used for this thesis were identified and approved.

The final STOP study protocol (version 4) (see Appendix 1) was submitted during the funding application process and subsequently reviewed by the ethics committee prior to commencement of the study (see sections 2.5.1 and 2.5.2).

4.6 Regulatory approvals

4.6.1 Ethics Approval

The National Research Ethics centralised system was used to apply for ethical committee review. It was anticipated that informed consent would not be required from participants included in the quantitative study but that consent would be required form women, their birth partners and the staff involved in the qualitative aspect of the study and not reported here. Ethical review was considered invaluable in terms of identifiers required to permit location of maternity records, and facilitation of access to medical records. The South East Coast Strategic Research Ethics Committee reviewed and approved the study (REC reference number 07/H1102/9; Appendix 2).

4.6.2 Research and Development (R and D) approval

Despite data collection not directly involving contact with women, because those data are held within NHS systems, local R and D approval was required prior to commencement of the STOP study. Approval was granted at each participating Centre (see Appendix 2).

4.6.3 Compliance with the Data Protection Act and information approvals

All access to and processes of data storage and use adhered to the Data Protection Act (HMSO, 1998) and Framework of handling identifiable patient information (Report of the Caldicott Committee, 1997) (www.dh.gov.uk). Discussions with the Caldicott Guardians for King's College London, and the two participating NHS Trusts, ensured imported data contained minimal identifiers to enable researchers to locate maternity records and obtain additional information to review and validate information entered electronically

4.7 Data collection

Prior to commencement of the study there was careful consideration for the methods and source of data collection to be undertaken. The majority of evidence regarding PPH is based on audit of routinely collected or summary clinical data (Zwart, 2009) or retrospectively collected data (Callaghan *et al.*, 2010; Knight *et al.*, 2009). Both approaches are associated with inherent limitations; it is commonly reported that routinely collected data, especially documented in emergency situations, are of variable formats, detail and quality.

Retrospectively collected data is associated with recall bias (Knight *et al.*, 2009; Claudius *et al.,* 2008).

It was decided that contemporaneous, expedient data collection was required to optimise data quality, facilitating prompt identification and investigation of omissions and inconsistencies in the information recorded. In both Centres maternity records comprised of a combination of paper and electronically recorded data. It was therefore necessary to expediently interrogate multiple sources of information, from handheld maternity records to specific databases used within the NHS, such as Results Reporting Service (RRS, for biochemical and haematological results), ultrasound and radiology reports (ASTRIA™) and blood transfusion records (electronic and paper) in addition to the electronic summary data in each unit (Healthware™ and EuroKing™).

The method used by the annual Scottish Confidential Audit of Severe Maternal Morbidity was considered. This is a paper based reporting system where predefined events are investigated locally by designated staff members in each participating Centre (most commonly Risk Managers). Requisite data collection forms are completed and sent, by post, to the Audit Management Centre in Aberdeen. Data are then entered onto a central database, and any inconsistencies or missing data queried and investigated prior to analyses. However, it was decided that this process was too slow and labour intensive, potentially prone to inputting errors and now superseded by internet based solutions (Feied *et al.*, 2004).

The availability of internet, high speed machines and secure servers made electronic data capture a more attractive and reliable method of gathering contemporaneous accurate information. The emergence of electronic patient records in all aspects of clinical health care and the potential for the sharing of contemporaneous and historical data to improve clinical care, providing data quality and consistency was assured (Hammond *et al.*, 2003; Boyle and Cunningham, 2002) also informed the study design. Electronic patient records are advocated in numerous countries, including England (Protti, 2007) where the slow progress in introduction is due to political and contractual issues, rather than commitment to this mode of record keeping (Robertson *et al.*, 2010). Furthermore the experience of the Division of Women's Health, Kings College London and King's Health Partners of using electronic data management for all clinical trials since 2003 (Baker *et al.*, 2009; Poston *et al.*, 2006) further supported the use of electronic data capture as the modality of choice for the current study.

Negotiations with MedSciNet[AB], a leading provider of Internet based web solutions for clinical registers and trials, confirmed that anonymised data importation would be possible from most existing system formats, including the commonly used maternity specific data systems employed within the NHS e.g. Healthware (Terranova)™ (used at Centre 1) and HSS EuroKing™ (used at Centre 2). Discussions with the NHS managers responsible for the information technology in participating Centres, confirmed that importation of clinical data with minimal identifiers to maintain confidentiality was possible. This involved processing the information through a series of filtration silos, with different levels of access, to maintain confidentiality and security. This approach still provided sufficient information for research midwives to identify the maternity notes. A secure

internet based data management system was developed with the address www.medscinet.net/stop. Figure 4.2 shows the public front page was created for the database, although a secure password was required to login and access the site.

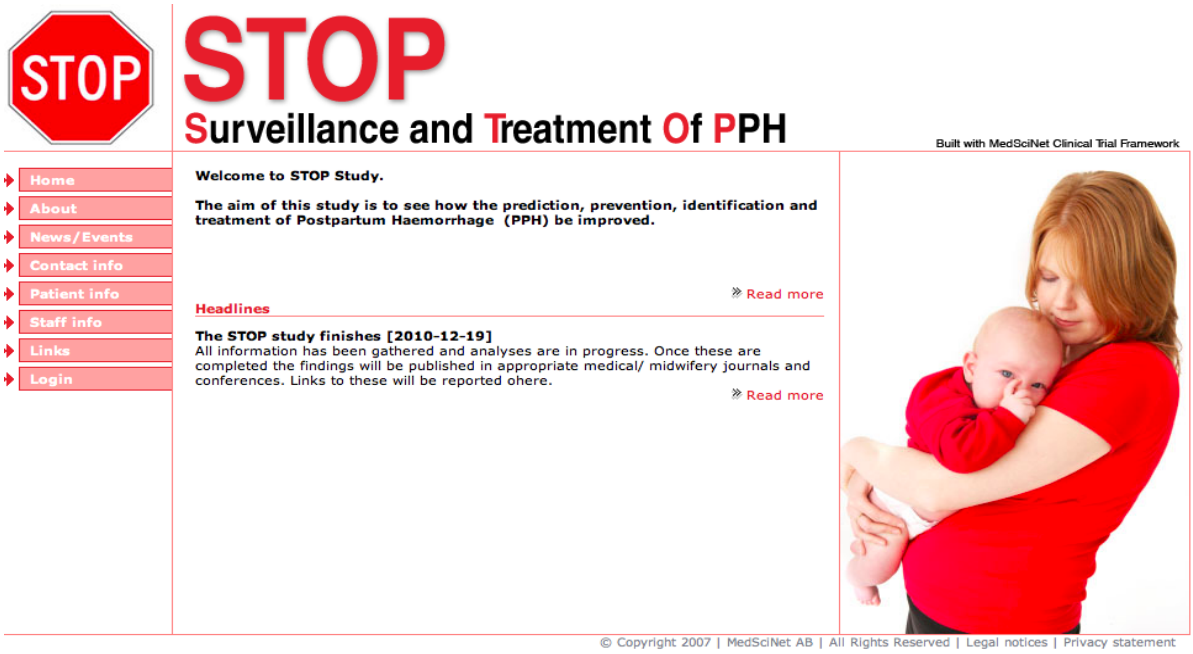


Figure 4.1: Public page of STOP study website.

4.7.1 Database access

Authorised users had variable degrees of access in order to maintain confidentiality. Each access required a user name and individual password that needed updating every 3 months. This enabled unit users to view and enter data for a single site. Global access allowed all data to be viewed and summary data to be extracted, and the global administrator was allowed the same access rights as global user, but additionally could add data options as required (for example conditions added to drop down boxes). All database activity was recorded in an

audit trail. A further user status, "view all" enabled those granted this access to see all data but no ability to enter or edit it. Members of the advisory group could therefore view the data contemporaneously throughout the duration of the study.

4.7.2 Importation of data from NHS systems

The first level of access is "Unit User". After entering an individual login and password, this allows authorised individuals to view the imported summary data for all women giving birth in one Centre. Separate passwords are required for each Centre.

An additional password was required to view more detailed summary information for those women randomly selected according to the weighting strategy. Imported data were not entirely consistent, due to variance in routinely collected information in each Centre, and the format of information entered onto EuroKing™ and Healthware™; for example, pain relief in labour was collected in Centre 1 but not available for import in Centre 2. Where erroneous imported data were discovered, corrections were made in accordance with reviewed case notes and other available data. All analyses were undertaken according to re-catagorised estimated blood loss.

Figure 4.3 shows the mechanisms employed to import select and review maternity records to ascertain documented blood loss, and the processes employed to confirm volumes.

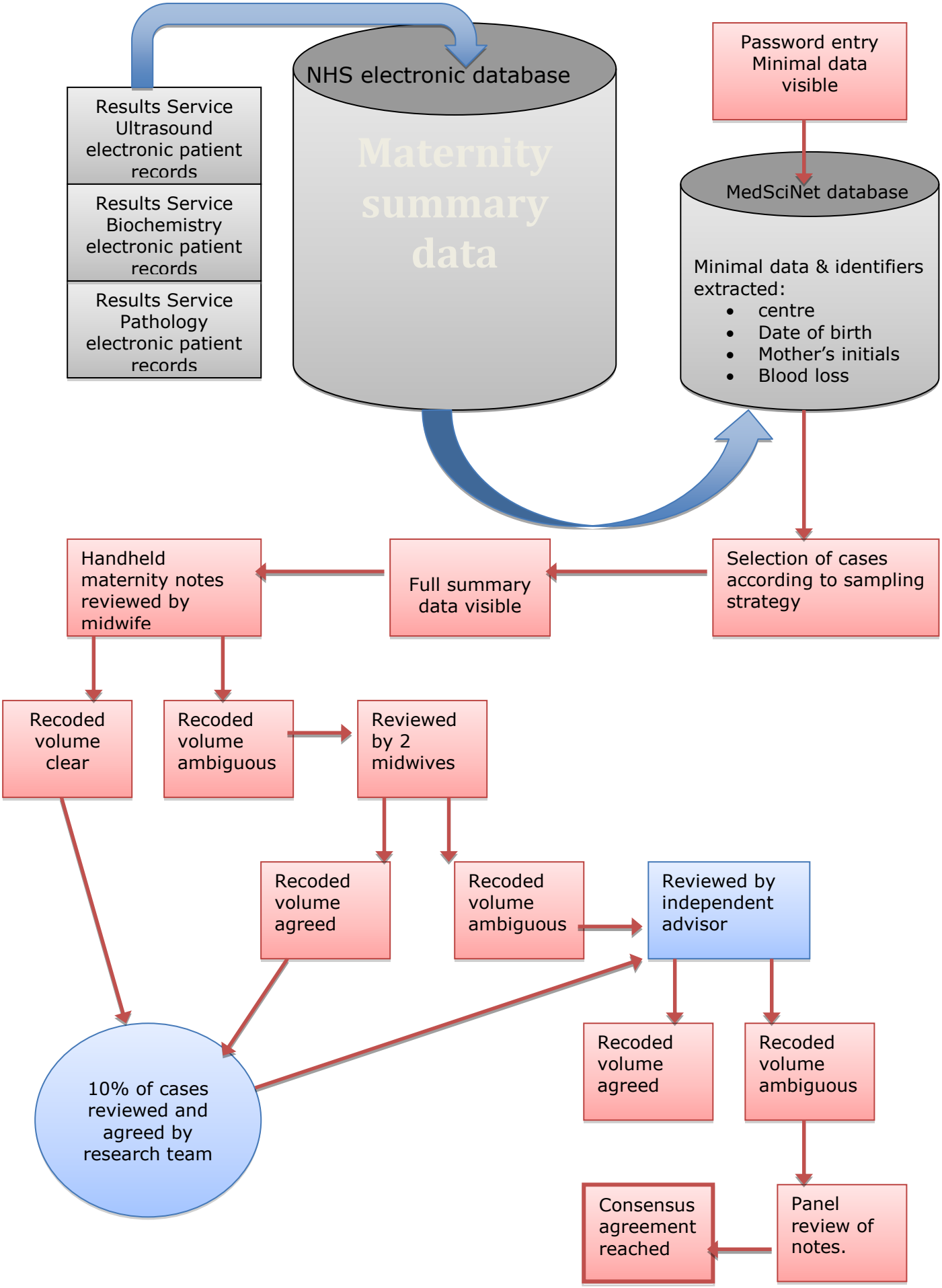


Figure 4.2: Flow diagram of note selection and review processes

4.8 Data variables

4.8.1 Selection of data variables to be imported from NHS electronic patient records

Relevant data variables were selected for importation into the research database are shown in Appendix 3. These were selected to 1) facilitate identification sufficient to enable location and review of all relevant patient notes, or 2) on the basis of previously reported risk factors.

4.8.2 Selection of outcome variables to be reviewed in weighted sample

Outcome variables accessed from data sources for reviewed cases were selected following review of the available literature and discussion with the STOP study advisory group. Many were identified as relevant to the changing demography of childbirth, and therefore potential contributors to the temporal rise in PPH (Knight *et al*., 2009; Ford *et al.*, 2007).

Primary outcome variables related to estimated blood loss and information regarding this was collected in multiple ways to maximise accuracy. However, only documented blood loss volumes were included, as arbitrary application of a specified blood loss volume, for example when lochia was recorded as "heavy", or "clots" would make accurately quantifying total volume impossible, and potentially introduce ascertainment bias, However this policy could potentially mean that all volumes are underestimated.

It was anticipated that blood volumes lost would be both over and underestimated (Larsson *et al.*, 2006; Glover, 2006). Therefore factors associated with estimation were selected in an attempt to investigate the true incidence of PPH, to ascertain frequency and scenarios for measuring blood loss and identify recording errors. Irrespective of documented blood loss, these factors included actions taken in response to PPH, date and time of documentation of PPH in maternity records, receiving of blood or blood products and the number of units given, admission to higher levels of postnatal care (high dependency unit or intensive care unit, due to differing facilities in participating Centres) and, antenatal haemoglobin (Hb) level preceding birth and postnatally. In women with an available antenatal Hb within 6 weeks prior to giving birth, a fall of 4 grams per litre (g/l) between this and the third day postnatal result, in women not in receipt of blood or blood products, was defined as "probably PPH". Although difficult to locate evidence for, anecdotally and clinically, a fall of 2 g/l is commonly considered indicative of a 500 ml blood loss. We therefore estimated 4 g/l indicated at least 1000 ml loss and therefore constituted "probably PPH". Other outcome variables were selected on the basis that they may increase or ameliorate blood loss at birth.

4.8.3 Ordering of variables: determination of risk factors for PPH

Variables were ordered sequentially and chronologically. It was assumed that earlier events could affect those occurring later, but the reverse was not possible. These are described, with the rationale for inclusion in Appendix 3.

Previously identified and *de novo* risk factors were assessed in three categories:

a) Pre-pregnancy: socio-demographic (maternal age and ethnicity); local deprivation (The Index of Multiple Deprivation 2007 combines a number of indicators, chosen to cover a range of economic, social and housing issues, into a single deprivation score for each small area in England. It covers seven aspects of deprivation, [i) income, ii) employment, iii) health deprivation and disability, iv) education, skills and training v) barriers to housing and services, vi) crime, vii) living environment], to produce a single deprivation score for each small area of England. www.gov.uk/government/collections/english-indices-of-deprivation); general and medical risk factors (BMI, pre-exiting medical conditions); obstetric history (previous PPH, previous CS, parity).
b) Pregnancy acquired/ developed: first antenatal appointment data (gestation at booking, BP, smoking status); antenatal day unit attendances (number and reasons); placenta praevia (diagnosis and location); urinary tract infection (gestation, number and treatment); gestational hypertension, pre-eclampsia, polyhydramnios and anaemia; medications pre-birth.
a) Birth and the third stage of labour: gestation at birth, birth weight, onset of labour; intrapartum (duration of ruptured membranes, Prostaglandin E_2 dinoprostane (Prostin®) use); maximum maternal temperature in labour, evidence of chorioamnionitis, oxytocin (Syntocinon®) use, spinal/epidural anaesthesia/analgesia; delivery (mode); management of third stage of labour; retained placenta; interval to suturing.

A complete list of the imported data variables and outcome variables, definitions of categories, variables and terms, outcomes, exposures, risk factors, potential

confounders, effect modifiers and the diagnostic criteria selected are listed, in alphabetical order, in Appendix 3.

4.8.4 Non-specified, descriptive and repeated variable data entry

It was decided that to enable additional data entry on three occasions (extraction comments, pre-existing maternal medical conditions and pregnancy acquired conditions) a limited number (ECRIN, 2007) of free text boxes were necessary to capture additional relevant clinical information.

Ease of abstraction of relevant data was paramount, therefore any repeated variables, for example antenatal admissions, were entered in chronological order, with the gestational age at admission recorded. For each admission duration of stay was not recorded, as this was considered subjective in terms of management and social situation, and not necessarily attributable to severity of maternal condition. The exception, due to association with abnormal placentation and prediction of postpartum haemorrhage, was admissions for antepartum haemorrhage (APH). However, as minor vaginal bleeds during pregnancy are common, the degree of bleeding was captured using a selection of drop down box options which included: spotting, light, like a period, heavy/clots, heavy/transfusion required. Further drop down options regarding the cause of bleeding were: unknown, placenta abruption, placenta praevia, local genital tract, fetal bleeding, low-lying placenta, other.

Drop down lists were used where appropriate to expedite data entry but also reduce the typographical errors, which complicate data cleaning prior to analyses. These included reasons for induction of labour, CS and causes of PPH.

As documentation in emergency situations has been criticised in terms of accuracy of timings (Knight *et al.,* 2009; Claudius *et al*., 2009; Winter *et al*., 2007), it was decided to record actions undertaken in the order they were executed and not record the time of administration. All actions were entered via drop down boxes as described above.

Blood test information pages were generated by clicking the "additional blood info" icon on the navigation tree, thus as many as were required could be generated, with no upper limit applied. The date and time of each test was entered initially and the results sorted into chronological sequence by the computer programme, thus providing an accurate time/result continuum, regardless of the order of test entry. This was considered important, as results are not always filed sequentially in medical records.

Experience of attending clinicians has been cited as important in various reports (Lewis, 2007b), therefore the database was designed to capture the grade of staff involved in managing any PPH. Due to the observational nature of the study and the importance of a no-blame culture it was decided that tick boxes noting all personnel involved would be the most appropriate method to collect these data.

4.9 Database Piloting

The process of data importation, whilst theoretically possible, had to be tested, to ensure regular downloads from NHS computer systems, completeness of imported data and the employment of appropriate, but minimal, identifiers to enable location of the handheld maternity notes for selected cases. Therefore data were imported, from one Centre, for two months (01/06/2008 to 31/07/2008) and all processes of data review piloted. During this time the list of options for numerous drop down boxes were altered and increased to reflect the data recorded in the handheld maternity notes. The chronological ordering facilitated data entry, the system of identifying missing and incomplete data further aiding data completeness.

4.10 Data entry processes to ensure data consistency and quality/data cleaning

Each database page contained a "save draft" and "save" function, this enabled data to be checked, and pages commenced where certain points required verification, using the NHS results database for example. In the patient overview window pages with no information entered appeared as white, those with some data entered, but requiring additional information or confirmation, were yellow, and completed data pages appeared as green. This facilitated identification of missing data. Additionally an "alert" system identified missing and incomplete data, which could be accessed via the "alerts" tab on the database.

Due to the limited number of people entering data the potential for erroneous data entry was low. Ongoing contemporaneous inter-user assessments were undertaken throughout the period of data collection. All ambiguous data and discrepancies, and 10% of all notes, were further reviewed independently (by Dr

Graham Tydeman, NHS Fife). Where assessment of total volume lost varied between researchers by >5%, the researchers undertook further review and discussion led to a consensus decision. Had this not been achievable, Professor Susan Bewley (CI) would have arbitrated, however this was never required.

4.11 Data analysis

All analyses were undertaken using revised data and Stata version 11.2 (Stata Corp, College Station, Texas USA). Summaries, estimates and comparisons were calculated using proportional weighting to adjust for the sampling plan. The variables were analysed in sequential order grouped in 3 broad categories: a) pre-pregnancy, b) pregnancy acquired and c) labour, intrapartum and third stage management. Throughout the results, both the number of women involved (n), and the number represented (nw) are shown.

4.11.1 Grouping of estimated blood loss into categories: assessment of incidence of PPH

Mean millilitres (ml) of blood volume loss may be less important than thresholds, which are triggers or prompts for actions in terms of monitoring, reporting and treatment. In order to calculate the incidence of PPH at various thresholds, and compare with other historical and contemporaneous data, imported and total estimated blood loss for each woman was therefore categorised as:

i) Missing

ii) 0- 24 ml

iii) 25-499 ml- no PPH

iv) 500-999 ml- minor PPH

v) 1000-1499 ml- moderate PPH

vi) ≥1500 ml- severe PPH, further divided: 1500-1999 ml; 2000-2499 ml; ≥2000 ml; ≥2500 ml

4.11.2 Initial statistical methods

Descriptive statistics were used to summarise the data and presented as proportions for estimated blood loss error rates (Chapter 6), population demographic characteristics, days of the week and time of delivery and blood loss at different thresholds (Chapter 6). Time of delivery was grouped in 3 hour segments (00.00- 02.59; 03.00- 05.59; 06.00-08.59; 09.00-11.59; 12.00-14.59; 15.00-17.59; 18.00-20.59; 21.00-23.59), as this was considered discrete enough to identify differences that could be missed with both smaller and larger time frames. These also meant that staff 'change-over' did not occur on the cusp in either Centre for midwives, ancillary or medical personnel. Confidence intervals were included for incidence of estimated blood loss at different thresholds (as described above). Geometric mean and medians were calculated for estimated blood loss categories to investigate differences by Centre. Geometric mean was calculated because of the positive skew apparent in non-symmetrical data. The inclusion of a small number of high values means the distribution tail is longer on the right hand side, leading to inflation of the arithmetic mean. Geometric mean is calculated using log-transformed data; the arithmetic mean is then calculated using the created log transformed scale, which can then be back-transformed to give a mean in the same units as the original data (Peacock and Peacock, 2011).

The arithmetic mean is appropriate whenever the total is an important concept, for example total wages bill, total cost total number of employees. The total blood loss across many different pregnancies carries no meaning. For a log-normal

distribution the geometric mean is more stable and being close to the median is a better representation of the typical woman's experience. Mean estimated blood loss and Odds Ratios were calculated for mean change in estimated blood loss and PPH≥500 ml in all women and ≥1000 ml and ≥1500 ml in women who bled at least 500 ml.

4.12. Development of regression models

Multiple regression analyses were used to investigate the predictors of blood loss. Logistic regression analyses were required to investigate PPH and progression to severe PPH where the outcome variables are categorical (as opposed to linear) and therefore simple linear regression models would be inaccurate (Field, 2009). Logarithmic transformation of the data enables a non-linear relationship to be expressed in a linear way overcoming the problem of violating the assumption of linearity (Field, 2009).

Three series of hierarchical regression models were developed to investigate:
1) mean estimated blood loss, 2) estimated blood loss ≥500 ml, 3) estimated blood loss ≥1500 ml. Variables were included chronologically, with those failing to reach statistical significance at each stage dropping out of the model (see explanation below). Whilst it could be argued that all variables should remain, models work best with reduced numbers of cells and therefore inclusion of non-significant variables would inhibit the performance of the prediction model. Consequently a trade off is required between inclusion of all possible variables and minimising the number of cells within the model to enhance the predictive performance of it.

The initial model used linear regression, with the outcome estimated total blood loss in ml, and undertaken using the representative sample. Secondly, logistic regression analysis investigating estimated blood loss ≥500 ml (all PPH) using the representative sample. Thirdly, logistic regression with the outcome, estimated blood loss ≥1500 ml, using a reduced data set comprising of those women with estimated blood loss ≥500 ml (all those with no PPH, EBL<500 ml were excluded from this model), to identify factors leading to progression from mild to severe PPH.

In each case, a series of models were fitted: firstly estimating the role of variables in category 1 (pre-pregnancy); then category 2 (pregnancy and labour) adjusting for group 1; then category 3 (birth and third stage) adjusting for groups 1 and 2 and iteratively for all 15 subgroups. The lists were reduced in size at each stage by fitting new variables singly and removing non-contributory variables shown not be related to outcome. In this way, adjustment was made for potential confounders at each stage (Herman *et al.*, 2002).

Three variables required alternative models to be fitted to determine the most appropriate method of characterising them. These were: temperature, measured in degrees centigrade above 37, with normal characterised as 0; placenta praevia, characterised as anterior, posterior, major and minor, was considered as a potential predictor of PPH; antepartum haemorrhage, characterised as APH or "warning APH" (recurrent, at least 3 occasions, like a period or heavier and placental).

No formal adjustment was made for multiple testing or colinearity (Perneger, 1998; Rothman, 1990) as a single primary endpoint was not relied upon; the totality of the evidence from a number of related sources was considered with the most weight put on the most significant results. Adjustments focus on a number of null hypotheses being simultaneously true and interpretation relies on the cumulative results of multiple tests. Problems with tests have been explored in detail in the literature and deemed not suitable for epidemiological studies (Perneger, 1998). All principal conclusions were supported by a number of related tests, usually at levels beyond $p<0.001$.

4.13 Comparison with previous and contemporary datasets

Comparison with historical data obtained 1997-1998 from the same hospital Trusts for the two STOP study sites (Waterstone *et al.,* 2001) was undertaken to identify changes in severe PPH rates with time, using an identical definition. An additional comparison of major haemorrhage rates (≥2500 ml) was made between study data and a contemporary cohort from the 2009 Scottish Audit of Severe Morbidity (Lennox and Marr, 2011).

4.14 Summary

The impact of duplication of data caused by transcribing from paper records to NHS summary data has not been identified previously. The current study facilitates error rates to be calculated for estimated blood loss and other routinely collected data.

The investigation of known and propose variables and their relationship with mean blood loss and PPH at different thresholds maximizes comparison with other datasets.

The introduction of variables chronologically, acknowledging that earlier factors may influence subsequent events, but the reverse is unlikely, means that each variable and its association with PPH is considered in a logical sequence.

Prior to investigating the impact of variables on blood loss, it was necessary to look at the missing data and reported errors. These results are presented in Chapter 5.

Chapter 5: Missing data, estimation and reporting errors

Maternity records for detailed review were selected as described in Chapter 2: Methods.

5.1 Missing Data

No blood loss or EBL 0-24 ml was recorded on NHS summary data (Healthware™ or EuroKing™) for 133 (7%) women. Two women were excluded from analyses because there was no mention of blood loss in maternity records. Of the remaining 131 women, all but two, one with blood loss 0 ml documented in handheld notes, and the other had documented blood loss of 20 ml, were recategorised into higher blood loss categories following review of handheld maternity notes and NHS databases. Table 5.1 shows the distribution of these through the categories. Of these women with no reported blood loss in maternity summary data 22.5% had a PPH ≥500 ml and more than 8% lost ≥1000 ml.

Table 5.1: Recoding for 133 women where EPR stated no imported blood loss or volume 0-24 ml imported after review of the maternity notes.

Blood loss recorded in notes (ml)	Missing	1-24 ml	% of volumes represented
missing	2	0	0.77%
0-24 ml	2	0	0.77%
25-499 ml	98	1	75.8%
500-999 ml	19	0	14.62%
1000-1499 ml	6	0	4.62%
1500+	3	2	3.85%

5.1.1 Waterbirths

Water births proved difficult to classify, with acknowledged challenges of estimating blood loss in water (Garland and Jones, 1994). This was further confounded by Centre 2 where, in accordance with unit protocol, estimated blood loss at water birth was recorded as < 500 ml or > 500 ml. There were 101 recorded pool births (22 at Centre 1; 79 at Centre 2).

In 61 cases total blood loss could only be estimated within broad categories (<500 ml/>500 ml). These included 8 homebirths. The remainder were in alongside midwife led units (4 in Centre 1, 49 in Centre 2). Women were assigned to no PPH if EBL was documented as "normal", "<500 ml", or any volume <500 ml where there was no documented subsequent blood loss. Women who had initial and subsequent EBL totaling >500 ml were recatagorised accordingly. (57 women lost 25-499 ml, 4 lost 500-999 ml).

5.2 Differences between imported and notes review of estimated blood loss according to category

Table 5.2 shows the number of cases imported from electronic patient records (EPR) including 35 identified via blood transfusion services, according to category and recategorisation after review. Of the 4 'missing/<25ml', 2 were excluded from analyses, due to the absence of any documented estimated blood loss data (1 unattended birth; 1 attended by paramedics), and two were included because the attending midwives had documented "no blood loss", and it was considered this was as valid as any other volume estimated by attending clinicians.

Estimated blood loss was correctly recorded according to category 82% when EBL 25-499 ml; 87% when EBL 500-999 ml; 94% when 1000-1400 ml; 88% when EBL ≥1500 ml. Indicating similar error rates at all levels of estimated blood loss.

Table 5.2: Data imported from NHS electronic patient records, or blood transfusion services, according to estimated blood loss category for the selected weighted sample.

	Estimated blood loss (ml) corrected					
Imported Blood loss (ml)	Missing/<25	25-499	500-999	1000-1499	1500+	Total
Missing	2	98	19	6	3	128
0-24	0	1	0	0	2	3
25-499	0	537	12	0	3	552
500-999	0	5	372	13	4	394
1000-1499	0	1	5	453	22	481
1500+	0	0	1	3	298	302
Selected via blood transfusion	0	9	18	2	6	35
Total	2	651	427	477	338	1895

In summary, following review of the complete maternity records (handheld 'paper' and all electronic databases) relating to each woman, recoding was required in >12% of the cases reviewed. Table 5.3 shows the number and % of cases recoded into a different blood loss category that almost four times as many women in the sample group were recoded up compared to the number recoded down. This concurs with the findings of others investigating measured blood loss, that whilst overestimation can occur, underestimation is more common (Larsson *et al.,* 2006; Bose *et al.,* 2006). Thus suggesting such errors are evident in both measured and estimated blood loss.

Table 5.3: Records recoded to a different category after review of the handheld maternity notes.

Blood loss category	Frequency	Percentage (%)	Cumulative
Recoded down	50	2.64	2.64
Unchanged	1662	87.70	90.34
Recoded up	183	9.66	100.00

5.3 Validation of reviewed data

All randomly selected notes were reviewed independently by one of two members of the research team (Annette Briley/ Henrietta Ballard). Any ambiguous cases were discussed, and where agreement could not be reached, were reviewed independently by a member of the Study Advisory Group (Graham Tydeman). Additionally every 10th set of notes was further scrutinised by the reviewers to ensure inter-observer validity (Uebersax, 1989). Where there was >10% difference in the volumes documented, discussion between the reviewers led to consensus agreement of volume lost. Total number of notes discussed by 2 or 3 researchers was 213. A sample of this process can be seen in Figure 5.1. Final arbitration with the study CI was never required.

ID	Initials	EBL as imported	GT best estimate	EBL as saved	revised to	discussed and altered values	Comments from GT
445	db	1200	1200	1200			peripartum loss - abruption, therefore some APH
456	er	1000	1000	1500		1500 agreed as 2 modes of delivery anddifferent volumes recor	min/max 1000-1500
467	ap	2200	2000	2200			min/max 1500-2200
497	zk	1100	1135	1135			1100-1135
525	ln	3200	3200	3200			min/max 500-3200
568	so	755	1100	1100		GT happy with 1100	min/max 1100-1355
569	pf	500	400	900		GT agrees in view of overall clinical picture agrees 900	min/max 400-500
576	rn	2000	2000	2000			min/max 1155-2200
585	sz	1000	770	1100	1350	reviewed additional brisk loss found revised to 1350	min/max 770-1000
589	ac	2000	1900	2500	2000	reviewed consensus opinion 2000	min/max 1500-2000
630	ls	2000	2000	2000			1800-2000
635	td	1800	1800	2000			min/max 1500-1800
657	pa	2000	2990	2970			min/max 2000-2990
663	oo	800	800	800			exclude from study - mat death
665	hm	1731	1731	1731			
669	mk	blank	15350	15000			
679	ag	3000	3300	4000	3000	reviewed consensus agreement 3000ml	
684	jb	2000	2295	2000		went through again falls within rangeg identified by GT, happy t	1890-2790
713	ss	200	1900	1900			
723	dg	2000	2000	2000			
882	no	750	1500	1500			

Figure 5.1: An example of the spreadsheet indicating validation process.

Minimal identifiers, (study ID maternal initials), estimated blood loss as imported into study specific database from NHS electronic patient records, the next column indicated the volume as independently assessed (GT) the next column indicated EBL as calculated following review of medical records (AB/HB) if the estimated blood was revised the reasons are noted, and where consensus was difficult due to documentation a range was also noted,

When extrapolated to the population studied, after adjustment for documented estimated blood loss, >95% women remained in the same estimated blood loss category. Table 5.3a shows the percentage of women represented for whom these adjustments meant estimated blood loss category changed. The prevalence of under reporting remained, with 4.30% coded into a higher estimated blood loss category, compared with 0.76% who were recoded down.

Table 5.3a: Recoding according to category with the representative sample.

Estimated blood loss category	frequency	Percentage (%)
Recoded down	75	0.76
Unchanged	9435	94.94
Recoded up	427	4.30
Total	9937	100.00

When investigating errors by Centre, Table 5.4 shows Centre 2 more accurately estimated lower volumes of blood loss (00-499 ml) but Centre 1 more accurately recorded blood loss 1000-1499 ml. For blood loss ≥ 1500 ml, error rates in both Centres exceeded 40%.

Table 5.4: Represented sample (n) and percentage (%) requiring recategorisation of blood loss by Centre.

Blood loss category	Centre 1 n represented	%	Centre 2 n represented	%
00-499 ml	480/4261	11.26	121/2324	5.21
500-999 ml	302/1783	16.94	112/636	17.61
1000-1499 ml	92/403	22.83	54/139	38.85
≧1500 ml	127/286	44.4	46/105	43.81

5.4 Data quality and error rates

Handheld paper records are legally considered to be the "gold standard"; a concise, accurate, legible account of all symptoms, actions and treatments are clearly documented by attending clinicians (NMC, 2012). But from a research perspective have inherent issues regarding accuracy. Additionally summary data are often entered retrospectively onto NHS databases (Fawdry *et al.*, 2011; Boyle and Cunningham, 2002). Due to data variance and limitation, comparison between paper and electronic records was limited. Table 5.5 shows the error rates where available, and highlights discrepancies in data collected in different units. Centre 2 had far fewer obligatory summary data points than Centre 1. Similar errors were recorded for maternal date of birth (0.21% versus 0.19%). Maternal age had an error rate in Centre 1 (0.46%), but not in Centre 2; investigation revealed this was due to the system used in Centre 1 not automatically updating age following birthdays. There were no errors in baby's date of birth, however time of birth had an error rate of 0.2%-0.3%. Most commonly these were due to errors in recording the 24hour clock. Sex of baby could only be assessed in singletons due to confusion regarding birth order in multiple pregnancies, and the error rate was 0.41%. Mode of birth was incorrect in 1.97% of cases and birth weight in 2.03%. It was not possible to ascertain error rates in ethnicity due to the diversity of terminology used and data entered. Errors in blood loss data exceeded 12% (19.4% and 12.3%).

Table 5.5: All records where inaccuracies were corrected following review of the notes

Item Imported	Centre 1 n sampled= 1308 n represented= 6731				Centre 2 n sampled= 588 n represented= 3207			
	n	n (w)	%	% (w)	n	n (w)	%	% (w)
Maternal age	10	31	0.76	0.46	0	0	0	0
Maternal DOB	3	14	0.23	0.21	1	6	0.20	0.19
Ethnicity	*	*	*	*	*	*	*	*
Date of delivery	0	0	0	0	0	0	0	0
Time of delivery	6	28	0.3	0.42	1	6	0.17	0.19
Sex of baby (singletons) [total=1259]	6/1258* Excludes 1 interdetermin-ate assigned male on PM	27/6549	0.48	0.41	**	**	**	**
Mode of delivery (singletons)	34/1259	129/6561	2.70	1.97	**	**	**	**
Birth weight (singletons)	32/1259	133/6561	2.54	2.03	**	**	**	**
Blood loss***	254	1003	19.4	14.9	178	393	30.4	12.3

*ethnicity was reported too diversely to assess error rates.
**these data were not imported directly to the database from NHS systems
Date of birth, DOB.
*** These are the numbers of women and women represented who had blood loss volumes corrected, but did not necessarily change blood loss category. Of the 1895 (representing 9937) women described, 431 (1395) changed blood loss category, while 1464 (8542) did not.

5.5 Errors & typology of those errors: digit preference, threshold avoidance, threshold preference

Apparent in both electronic summary data and maternity notes tables 5.6 a, b, c, d and e show that a preference for recording estimated blood loss volumes ending in 10 and 50 ml was prevalent in all blood loss ranges in both Centres. This is particularly apparent in Centre 2 where no volumes were recorded between 100 ml and 150 ml as shown in Table 5.6a.

Table 5.6a. Digit preference and threshold avoidance for no postpartum haemorrhage.

EBL ml	50	100	120	140	150	160	170	180	200
Centre1	108 (1.60%)	60 (1.91%)	24 (0.36%)	12 (0.18%)	289 (4.29%)	12 (0.18%)	12 (0.18%)	0	676 (10.05%)
Centre2	60 (1.91%)	282 (8.86%)	0	0	316 (10.04%)	0	0	12 (0.38%)	552 (17.54%)

Estimated blood loss, EBL.

A disproportionate number of women have EBL at the thresholds 500 ml, 1000 ml, 1500 ml and 2000 ml see Tables 5.5b, c, d and e. This was also demonstrated at 2500 ml, but all numbers were small at this volume. Threshold preference is important because these thresholds are commonly described as "triggers" for further action in guidelines and protocols, which in turn have been advocated to improve patient care (Lyndon *et al*., 2010; Arulkumaran *et al*., 2009; Alfirevic *et al*., 2004). At these larger volumes, where blood loss should have been accurately recorded in accordance with national guidelines and local protocols (RCOG, 2009; Brace *et al.,* 2007; Stainsby *et al*., 2006), the majority of documented blood loss volumes ended in 0 or 5, which may be acceptable due to the precision achievable in measurement. However there was a disproportionate percentage at both 2000 ml and 2500 ml thresholds. In both Centres, volumes under a threshold were favoured over those above, although this was inconsistent across all thresholds.

Table 5.6b: Digit and threshold preference and avoidance around 500 ml estimated blood loss (EBL).

EBL ml	420	430	440	450	490	498	500	515	520
Centre1	12 (0.18%)	12 (0.18%)	12 (0.18%)	368 (5.47%)	6 (0.09)	0	594 (8.83%)	12 (0.18%)	1 (0.01)
Centre2	0	0	0	36 (1.14%)	0	12 (0.38%)	228 (7.24%)	0	0

Table 5.6c: Digit and threshold preference and avoidance around 1000 ml estimated blood loss (EBL).

EBL ml	960	970	979	985	990	1000	1005	1008	1010
Centre1	1 (0.01%)	6 (0.09%)	0	6 (0.05%)	6 (0.09%)	159 (2.36%)	0	0	1 (0.01%)
Centre2	0	0	6 (0.19)	0	0	53 (1.68%)	2 (0.06%)	1 (0.03%)	0

Table 5.6d: Digit and threshold preference and avoidance around 1500 ml estimated blood loss (EBL).

EBL ml	1450	1480	1490	1500	1505	1515	1520	1540	1550
Centre1	3 (0.04 %)	1 (0.01%)	1 (0.01%)	64 (0.95%)	0	0	0	1 (0.01%)	1 (0.01 %)
Centre2	0	0	0	24 (0.75%)	6 (0.19%)	1 (0.03%)	1 (0.03%)	0	0

Table 5.6e: Digit and threshold preference and avoidance around 2000 ml estimated blood loss (EBL).

EBL ml	1850	1870	1887	1900	1955	2000	2015	2050	2065
Centre1	3 (0.04%)	0	0	15 (0.22%)	1 (0.01%)	53 (0.79%)	0	1 (0.01%)	0
Centre2	0	1 (0.03%)	1 (0.03%)	3 (0.10%)	0	11 (0.35%)	1 (0.03%)	0	1 (0.01%)

5.5.1 Threshold preference

Table 5.7, shows the effect of threshold preference, looking at the incidence of PPH at various thresholds using the definition "equal to or more than" (Table 3.7a), compared with "more than" (Table 3.7b), in each Centre and combined in uploaded electronic data and in reviewed data.

Overall, when using the definition ≥, the incidence increased disproportionately for the additional 1 ml of estimated blood loss. In the imported data the incidence was significantly more when using this definition (≥), 32.3% versus 23.9% at 500 ml and 33.9% versus 25.6% in reviewed data. This was repeated at all thresholds (1000 ml: imported 8.0% versus 5.9%, reviewed 9.4% versus 7.3; 1500 ml imported 3.1% versus 2.3%, reviewed 4.0% versus 3.1%; 2000 ml imported 1.0% versus 1.3%, reviewed 2.0% versus 1.3%; 2500 ml imported 0.7% versus 0.6%, reviewed 0.8% versus 0.6%).

Table 5.7: Incidence of estimated blood loss at different thresholds, using the definition "equal to or more than (≥)" at each threshold (data entered by clinical staff, and following review).

	Centre 1	**Centre 2**	**All**
As imported			
Geometric mean	375 (392 to 359)	299 (321 to 278)	349 (363 to 336)
Median (Quartiles)	400 (IQR 250 to 550)	300 (IQR 200 to 500)	350 (200 to 500)
Normal estimated blood loss (no postpartum haemorrhage)	65.4% (62.3 to 68.4)	72.8% (68.5 to 76.6)	67.7% (65.2 to 70.1)
≥ 500 ml	34.6% (31.6 to 37.7)	27.2% (23.4 to 31.5)	32.3% (29.9 to 34.8)
≥ 1000 ml	8.7% (7.8to 9.7)	6.4% (5.4 to 7.6)	8.0% (7.3 to 8.7)
≥ 1500 ml	3.2% (2.8 to 3.7)	2.8% (2.2 to 3.5)	3.1% (2.7 to 3.5)
≥ 2000 ml	1.5% (1.2 to 1.9)	1.4% (1.0 to 1.9)	1.5% (1.2 to 1.7)
≥ 2500 ml	0.7% (0.5 to 0.9)	0.8% (0.6 to 1.2%)	0.7% (0.6 to 0.9)
As validated			
Geometric mean	395 (414 to 377)	305 (328 to 284)	349 (363 to 336)
Median (Quartiles)	400 (IQR 250 to 600)	300 (IQR 200 to 500)	350 (IQR 200 to 545)
Normal blood loss	63.3% (60.1 to 66.4)	72.1% (67.8 to 76.0)	66.1% (63.5 to 68.6)
≥ 500 ml	36.7 % (33.6 to 39.9)	27.9% (24 to 32.2)	33.9 (31.4to 36.5)
≥ 1000 ml	10.2% (9.0 to 11.4)	7.8% (6.4 to 9.4)	9.4% (8.5 to 10.4)
≥ 1500 ml	4.3% (3.5 to 5.2)	3.3% (2.6 to 4.3)	4.0% (3.4 to 4.6)
≥ 2000 ml	2.2% (1.7 to 2.9)	1.4% (1.0 to 1.9)	2.0% (1.6 to 2.4)
≥ 2500 ml	0.8% (0.6 to 1.1)	0.8% (0.6 to 1.2)	0.8% (0.7 to 1.0)

Table 5.7a: Incidence of estimated blood loss at different thresholds, using the definition "more than (>)" at each threshold (data entered by clinical staff, and following review).

	Centre 1	Centre 2	All
As imported mean (Standard Deviation)			
Geometric mean	375 (392 to 359)	299 (321 to 278)	349 (363 to 336)
Median (Quartiles)	400 (IQR* 250 to 550)	300 (IQR 200 to 500)	350 (IQR 200 to 500)
	% (95%CI)	**% (95%CI)**	**% (95%CI)**
Normal estimated blood loss (no PPH)	74.0% (71.3 to 76.5)	80.7% (77.1 to 83.8)	76.1% (74.0 to 78.1)
>500 ml	26.0% (23.5 to 28.7)	19.3% (16.2 to 22.9)	23.9% (21.9 to 26.0)
> 1000 ml	6.4% (5.7 to 7.1)	4.8% (4.0 to 5.8)	5.9% (5.3 to 6.5)
> 1500 ml	2.4% (2.0 to 2.9)	2.2% (1.7 to 2.8)	2.3% (2.0 to 2.7)
> 2000 ml	0.9% (0.7 to 1.2)	1.1% (0.7 to 1.5)	1.0% (0.8 to 1.2)
> 2500 ml	0.5% (0.3 to 0.7)	0.7% (0.4 to 1.0)	0.5% (0.4 to 0.7)
Following review			
Geometric mean	395 (414 to 377)	305 (328 to 284)	349 (363 to 336)
Median (Quartiles)	400 (IQR 250 to 600)	300 (IQR 200 to 500)	350 (IQR 200 to 545)
Normal estimated blood loss (no PPH)	72.2% (69.3 to 74.8)	79.3% (75.7 to 82.6)	74.4% (72.2 to 76.6)
> 500 ml	27.8% (25.2 to 30.7)	20.7% (17.4 to 24.3)	25.6% (23.4 to 27.8)
> 1000 ml	7.9% (6.9 to 9.0)	6.1% (4.9 to 7.5)	7.3% (6.5 to 8.2)
> 1500 ml	3.3% (2.6 to 4.1)	2.6% (2.0 to 3.4)	3.1% (2.6 to 3.7)
> 2000 ml	1.4% (1.0 to 2.0)	1.0% (0.7 to 1.5)	1.3% (1.0 to 1.7)
> 2500 ml	0.6% (0.4 to 0.8)	0.7% (0.4 to 1.0)	0.6% (0.5 to 0.8)

*IQR interquartile range

5.6 Place of birth

To further investigate influences on estimated blood loss and in the light of a recent report, analyses were undertaken investigating influence of place of birth (Birthplace in England Collaborative Group, 2011). However intended place of birth was not recorded, so direct comparison was hampered.

The majority of women (78.6%) gave birth in obstetric units 5348/6732 (79.4% Centre 1) 2461/3205 (77.8% in Centre 2). Alongside midwife led units (MLU)

existed in both Centres and 18% of women delivered there (16.6% in Centre 1; 21% in Centre 2), concurring with recent estimates that around 1:20 women give birth in these along side or freestanding units (www.health.org.uk).

The homebirth rate was 2.5% (245/9936) comparable to the average for England (2.49%) (Birthchoice, 2010), although there were significantly more in Centre 1 (198/6731 2.9%) than Centre 2 (47/3205, 1.4%), a reflection of typical variance across England (0.1% to 11.4%) (Birthchoice, 2010, www.birthchoiceuk.com).

Women delivering at home or in the MLUs were not at increased risk of PPH≥500 ml, concurring with the findings of others (Birthplace in England Collaborative Group, 2011) and shown in Table 5.8. There was also no increased risk of PPH ≥1500 ml, in either Centre 1 [OR 0.48, 95% Confidence Intervals (CI) 0.15 to 1.51, p= 0.212] or Centre 2 (OR 0.38, 95% CI 0.12 to 1.20, p=0.101).

Table 5.8: Postpartum haemorrhage (PPH) ≥500 ml in women giving birth at home or in midwife led units, by Centre and combined

Place of birth	**PPH≥500 ml** **Odds Ratio**	**95% CI**	**P**
Home birth	0.38	0.11 to 1.26	0.114
MidLed Unit (1)	0.80	0.49 to 1.30	0.37
MidLed Unit (2)	1.03	0.58 to 3.02	0.51
AMU*	0.90	0.60 to 1.37	0.64

Midwifery led, MidLed
* OR for deliveries in alongside midwifery unit, AMU (combined)

This was not the case for PPH ≥1000 ml, which was more likely in MLU Centre 1, (OR 3.15 [95%CI 1.38 to 7.17, p=0.006]) compared to MLU Centre 2, (OR 0.38

[95%CI 0.12 to 1.20, p= 0.101]). Despite the prevalence of African ethnicity in Centre 1, this difference is not entirely explained by ethnicity or parity.

5.7 Summary

One hundred and thirty one women had no information regarding blood loss entered onto NHS electronic data summary. Robust review of the notes showed that all but 2 women had estimated blood loss documented in the handheld maternity notes. Review of handheld maternity records and other information sources available regarding intrapartum care and blood loss, revealed visual assessment remains commonly the method of choice. In the current study no attempt was made to assess the accuracy of estimation of blood loss, but review of the data available showed further errors in the addition of documented volumes and failure to upload or edit estimated blood loss volumes onto electronic data systems. This study therefore has identified a further source of error, hitherto unreported or quantified. Whilst error rates for other routinely collected summary data range from 0.0-2.70%, those for estimated blood loss were much higher (12.3-19.4%).

The phenomena of digit preference and threshold avoidance previously described in relation to BP measurement are apparent when estimating blood loss. Recording volume ≥ a threshold, under estimates blood loss <500 ml and inflates estimated blood loss at all other thesholds.

With additional sources of errors identified the robust review system was required to ensure the completeness and quality of the available data within the constraints of visual assessment. Once the data were confirmed as complete as accurate as possible statistical analyses could be undertaken to investigate the

variables associated with mean estimated blood loss and PPH. These results are presented in Chapter 6.

Chapter 6: Results 1; Risk factors associated with mean estimated blood loss thresholds.

Sample selection is outlined with details of those excluded from analyses, and the handling of ambiguous data. Population characteristics in terms of incidence in the total population and relationship with PPH versus no PPH will be examined. Comparison with historical data in the same geographical locations and impact of place of birth, day of the week and time of birth will be presented.

6.1 Cohort and weighted sample details

The total number of deliveries in the participating Centres during the study period, 01st August 2008 to 31st July 2009, was 10,213 (Centre 1: 6721; Centre 2: 3492), which was within the 95% CI of the estimated annual deliveries represented by our sampling strategy (9938, 95%CI 9525 to 10333).

6.2 Exclusions

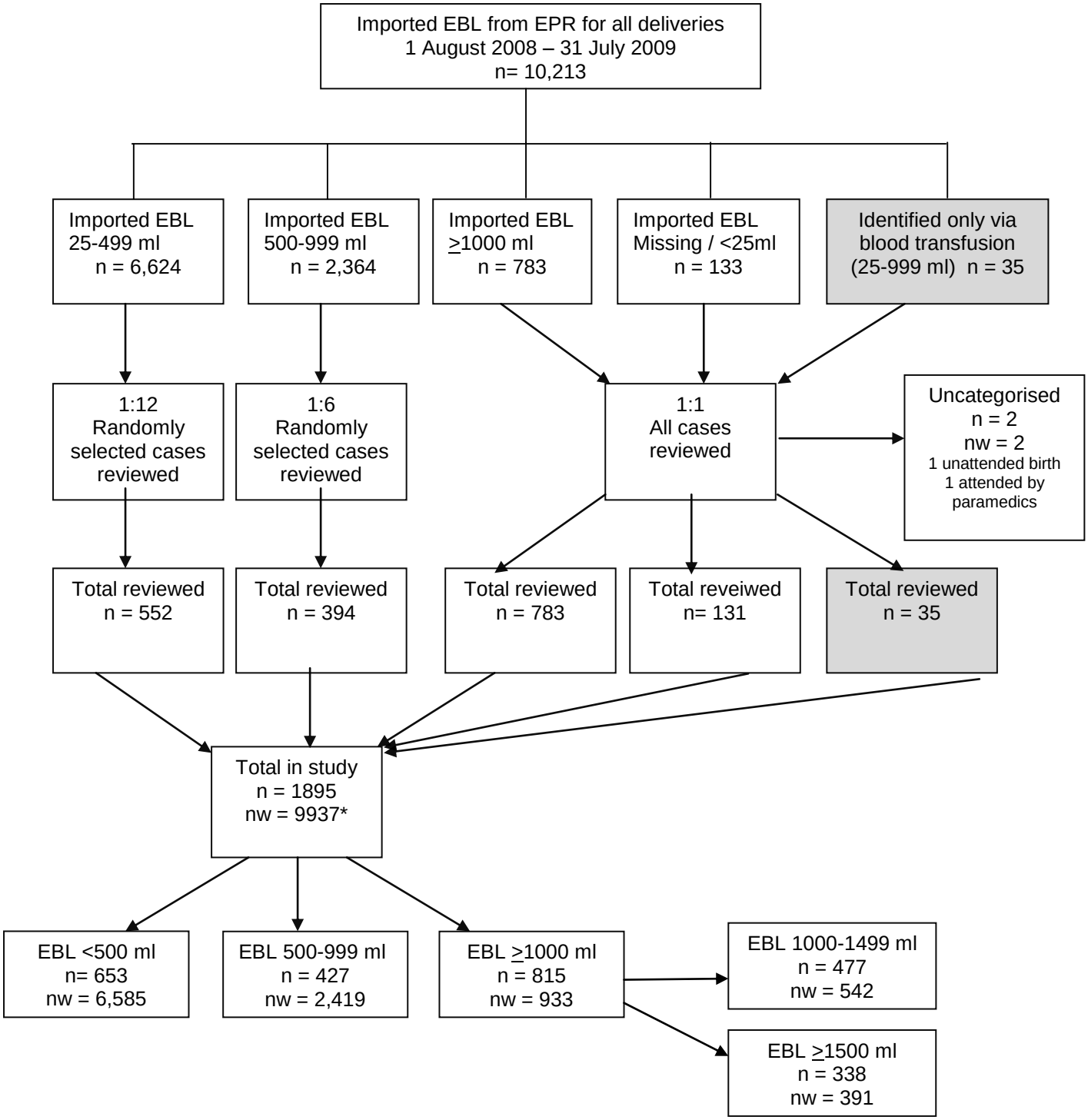
Following detailed review of the maternity records selected by weighting (n= 1897) two women were excluded from analysis, as there was no documentation regarding blood loss (1 unattended home birth; 1 attended by paramedics).

Review of the notes for women randomly selected according to the weighting strategy revealed a further woman (with reported estimated blood loss of 800ml) experienced an antenatal cardiac arrest and underwent emergency CS prior to maternal resuscitation, which was unsuccessful. It was decided to include her data regarding risk factors and incidence of PPH.

6.3 Sample size

Figure 6.1 shows 99.4% of sample (9,936/9,938) had sufficient data to assess estimated blood loss. The proportion of notes randomly selected according to imported estimated blood loss and those identified through blood transfusion records are shown with subsequent category revision following scrutiny of data sources.

Figure 6.1: STROBE diagram. Identification and classification of cases according to imported electronic patient records, recategorisation by estimated blood loss documented in handheld maternity notes, and sample weighting.



Shaded boxes demonstrate additional cases not identified through electronic patient records. EPR; electronic patient record; EBL, estimated blood loss; nw; number of women represented by the reviewed notes allowing for the weighted sampling. *Weighted sampling strategy represented population total of 9,937 (95%CI 9,532 to 10,340).

6.4 Demographic characteristics of the sample

Risk factors according to PPH category are shown as a percentage of the representative sample. Due to the weighted sampling strategy and proportional representation for differing estimated blood loss categories, combined with recoding, the number of women (n) in each category is not provided.

6.4.1 Pre-pregnancy factors and incidence of PPH

Table 6.1 shows the demographic characteristics and outcomes in women with and without PPH. In the whole cohort, 55% were aged ≥30 with 26% ≥35 years, indicating that this population was older than the general UK pregnant population at the time, reported as 47% aged over 30 years (ONS, 2010). Almost 60% were White, with Black African the largest minority ethnic group (17%). Whilst the percentage of White people is significantly less than the general population of England and Wales (>80%) the lower proportion is likely to be influenced by the proximity to London of the two participating Centres, where 45% of the resident population are White (ONS, 2011).

The Asian minority group is comparable to elsewhere in the UK (2.7%) (KSO6, 2009). Conversely the population in north Kent comprises 91.6% White, 3.5% South Asian, 2.0% Black, 1.7% Mixed race and 1.2% Chinese or other (www.dartford.gov.uk). Overall the study population was representative of the communities from which it was drawn. Thirty nine percent lived in areas of highest deprivation, influenced by the locality served by Centre 1 which is in the top 10% of most deprived London Boroughs (Trust for London, 2010). Conversely deprivation levels were lower than average around Centre 2 (www.apho.org.uk).

Just over half the women (51%) were primiparous, which is higher than reported in other datasets (www.birthchoiceuk.com) and may reflect the impact of Centre 1 as an inner city tertiary referral Centre.

More than 50% of women had a healthy BMI (defined as 19.0 to 24.9 kg/m^2), despite rising levels of obesity reported in the whole population (www.apho.org.uk; www.webarchive.selondonsector.nhs.uk). Over 22% were overweight (BMI 25- 29.9 kg/m^2) and >15% were obese (BMI≥30.0 kg/m^2). Twelve percent were cigarette smokers at first antenatal contact, less than in the general antenatal population (14%) (ONS, 2010).

Factors associated with PPH ≥500 ml were: maternal age 30-34, 35-39 and over 40 years, Black African ethnicity, Chinese ethnicity and primiparity. Conversely women aged <20 and 20-24 years, White ethnicity, BMI <19 kg/m^2 and cigarette smokers were less likely to experience PPH ≥500 ml.

Table 6.1: Characteristics of the study population by postpartum haemorrhage (PPH) (estimated blood loss ≥500 ml) or no PPH, following correction of errors, categorisation and weighting.

Demography	**No PPH**	**PPH ≥500 ml**	**All**
No. of women/notes reviewed	653	1242	1895
No. of women represented (nw)	6585	3352	9937
Age (years)	**% of population**		
<20	5.0	2.8	4.2
20-24	15.9	8.9	13.5
25-29	22.4	22.0	22.2
30-34	32.0	36.6	33.6
35-39	19.8	22.6	20.7
40+	5.0	7.2	5.7
Ethnicity			
White	61.2	55.3	59.2
Black British	2.4	1.0	2.0
Black Caribbean	4.4	4.2	4.3
Black African	14.2	22.3	16.9
Bangladeshi	2.0	1.1	1.7
Indian	3.0	3.8	3.3
Pakistani	3.7	3.9	3.7
Other Asian	0.7	0.9	0.8
Chinese	0.6	1.3	0.8
Mixed	3.0	1.6	2.6
Unknown	4.8	4.5	4.7
Body Mass Index (BMI) (kg/m^2)			
<19	6.3	4.8	5.8
19-24.9	50.8	51.2	50.9
25-29.9	22.3	22.3	22.3
30-34.9	10.3	11.9	10.8
35+	4.1	4.8	4.4
Index of multiple deprivation			
Quintile 1 (least deprived)	7.3	6.6	7.1
Quintile 2	9.8	10.1	9.9
Quintile 3	14.1	15.2	14.5
Quintile 4	29.5	28.0	29.0
Quniltile 5 (Most deprived)	38.8	39.3	39.0
Parity			
Primiparity	47.0	58.8	51.0
Smoking			
At booking	13.2	10.2	12.2
Previous obstetric history *(includes primiparous women)*			
No previous PPH	96.5	94.7	95.9
1 x previous PPH	3.5	4.8	3.9
>1 previous PPH	0	0.3	0.1
Previous Caesarean section	9.2	22.6	13.7
Pre-existing medical conditions			
Diabetes	0.9	1.2	1.0
Epilepsy (on medication)	0.4	0.7	0.5
Depression (on medication)	2.8	2.2	2.6
Hypertension	0.7	1.6	1.0
Fibroids	3.8	6.1	4.5
Female genital mutilation	2.8	3.3	2.9
Clotting or thromboembolic disorder	0.6	1.8	1.0
Uterine abnormality	0.2	0.3	0.2
Assisted conception	1.3	4.8	2.5
Current pregnancy			
Multiple pregnancy	1.8	4.0	2.6
Antenatal admissions	14.3	19.1	15.9

Any antenatal day unit attendance	47.3	53.6	49.5
Abdominal pain	15.7	17.2	16.3
Itching	2.0	2.3	2.1
External cephalic version	1.3	1.8	1.5
Pre-eclampsia screen	6.8	10.7	8.1
Reduced fetal movements	12.8	14.4	13.3
Possible spontaneous ROM	13.8	15.3	14.3
Generally unwell	3.1	3.8	3.3
Possible UTI	0.0	0.4	0.1
Vaginal bleed (no admission)	3.9	3.8	3.8
Placenta praevia	0.2	1.4	0.6
APH requiring admission	3.4	4.6	3.8
UTI (confirmed)	9.0	9.9	9.3
Gestational hypertension	2.1	4.6	2.9
Pre-eclampsia	0.9	4.3	2.1
Anaemia (Hb<10.5 g/ml)	12.4	14.1	12.9
Intrapartum			
Spontaneous onset of labour	74.7	51.3	66.8
Induced onset of labour	14.2	19.3	15.9
Augmented onset of labour	5.0	6.9	5.6
No labour elective Caesarean#	6.2	22.5	11.7
Temperature (>37.2°C)	12.3	27.8	17.3
Ruptured membranes >48 h	2.7	4.1	3.2
Dinoprostone	13.1	18.0	14.8
Oytocin (Syntocinon®) in 1st or 2nd stage	18.4	35.9	24.3
Birth			
SVD	76.1	25.9	59.2
Instrumental vaginal delivery*	12.1	17.1	13.8
Elective Caesarean section#	5.6	18.4	9.9
Emergency Caesarean section	6.2	38.6	17.1
Management of third stage of labour			
Physiological	9.2	3.4	7.2
Oxytocin (Syntocinon®) IM	7.3	5.4	6.7
Oxytocin (Syntocinon®) IV	13.4	58.1	28.5
Ergometrine Maleate/Oxytocin (Syntometrine®) IM	69.7	30.8	56.6
Retained placenta	1.3	4.4	2.4

Rupture of membranes, ROM; intramuscular, IM; intravenous IV. nw; Number of women represented by the reviewed notes allowing for the weighted sampling. *Forceps or ventouse; #Figures differ as some women planning elective Caesarean section had onset of labour, so Caesarean section classified as emergency.

6.4.2 Previous Obstetric History

Just over 4% of women had experienced PPH in at least one previous pregnancy, whilst traditionally identified as risk factor for excessive bleeding (Oyelese and Ananth, 2010; Ford *et al*., 2007), this was not associated with increased risk of PPH in the index pregnancy. Conversely previous CS was a potent risk factor for estimated blood loss exceeding 500 ml in subsequent pregnancies.

6.4.3 General health and medical factors and incidence of PPH.

Pre-existing medical conditions were relatively rare, affecting 0.5% (epilepsy) to 4.5% (uterine fibroids) of women. It should be noted that whilst relatively rare, the commonest pre-existing conditions in the study population are associated with a higher incidence in Black African/ Black Caribbean women (WHO, 2006b; Jolley, 2009).

The incidence of pre-existing epilepsy (0.5%), pre-gestational diabetes (2-5%) and lupus (0.2-1.0%) were comparable to those reported by others in antenatal populations (Diabetes UK, 2012; Mawhinney and Morrow, 2011; NICE 2008; Yasmeen *et al.*, 2001). Conversely essential hypertension (1%) and anaemia (0.8%) were lower than reported elsewhere (WHO, 2008; Sibai, 2002).

General health and medical factors associated with increased estimated blood loss ≥500 ml were: uterine fibroids, clotting or thrombotic disorders and assisted conception to achieve current pregnancy.

6.4.4 Current pregnancy

The incidence of multiple pregnancy was 2.6% compared with 1.6% for England and Wales in 2009 (ONS, 2010). Almost 50% of women attended ADU on at least one occasion, the most common reasons for attendance being abdominal pain (16.2%), suspected rupture of fetal membranes (ROM) (14.3%) and reduced fetal movements (13.3%). Just over 16% had at least one antenatal inpatient night. Placenta praevia complicated 0.6% of pregnancies, despite the incidence of previous Caesarean birth being 13.7%.

Pregnancy acquired risk factors that increased risk of PPH ≥500 ml included; multiple pregnancy, antenatal admissions, antenatal day unit attendances, pre-eclampsia screen, gestational hypertension and pre-eclampsia.

6.4.5 Labour and birth factors and incidence of PPH

Induction of labour rate was 15.9%. When combined with the augmentation rate of 5.6%, this is similar to reported induction rates of around 20% (www.birthchoiceuk.com; www.hesonliine.nhs.uk). Almost a quarter of all women received Oxytocin (Syntocinon®) in the first and/or second stage of labour.

Overall the CS rate was 27% (10% elective and 17% emergency), slightly higher than the national rate for England (24.8%) (www.birthchoiceuk.com). Conversely these national data reported a slightly lower rate of instrumental vaginal deliveries compared to the current study (12.5% versus 13.8%). The spontaneous vaginal delivery rate in these data was 59.2%, higher than the 41.8% reported for England (Birthchoice, 2010, www.birthchoiceuk.com).

The majority of women (91.4%) were given uterotonic drugs as part of active management of the third stage (AMTSL). The majority of women (56.4%) received Ergometrine Maleate/Oxytocin (Syntometrine®), with just over a third (35%) receiving Oxytocin (Syntocinon®) (28.3% IV; 6.7% IM). The impact of Oxytocin (Syntocinon®) IM failed to reach significance, despite being the recommended drug to prevent PPH.

Intrapartum factors that increased risk of PPH ≥500 ml included: induction of labour, elective CS, maternal temperature >37°C, ruptured fetal membranes >48 hours before birth, dinoprostone pessary/gel, oxytocin (Syntocinon®) infusion in first and/or second stage, instrumental vaginal birth, elective CS, emergency CS, oxytocin (Syntocinon®) IV and retained placenta. Protective factors were: spontaneous onset of labour, spontaneous vaginal delivery (SVD) and prophylactic Ergometrine Maleate/Oxytocin (Syntometrine®) IM for management of the third stage.

In summary, the women in this cohort were older, more ethnically diverse, heavier, more socially deprived and more likely to be expecting their first child than general UK figures for the study time period. However there were no higher levels of pre-existing medical conditions, previous Caesarean birth or previous PPH. Management of labour, birth and third stage was no different to other UK reports. The impact of individual variables on estimated blood loss, less than and exceeding 500 ml, both confirms and disputes previous evidence, suggesting the emergence of some novel factors (assisted conception, temperature in labour) demonstrating the necessity to consider variables in combination, and the complexity of relationships between variables that influence PPH.

6.5 Incidence of PPH at different thresholds

Following adjustment for transcription errors, overall 33.7% of women in the sample had a PPH≥500 ml. Of these 9.4% ≥1000 ml; of these 3.9% ≥1500 ml and of these 0.8% ≥2500 ml. Table 4.2 shows incidence at various thresholds in order to facilitate comparison with other studies.

Table 6.2: Overall incidence of estimated blood loss by category and at different volume thresholds using ≥ as cutoff.

Category	Estimated Blood loss (ml)	All (%)	95% CI
No PPH	<500	66.3	63.8 to 68.8
PPH – All	≥ 500	33.7	31.2 to 36.2
PPH - Minor	500-999	24.3	22.0 to 26.6
PPH - Moderate	1000-1499	5.5	4.8 to 6.1
PPH - Severe	1500-1999	2.0	1.6 to 2.4
	2000-2499	1.1	0.74 to 1.5
	≥1500	3.9	3.3 to 4.6
	≥2500	0.82	0.63 to 1.0

Postpartum haemorrhage, PPH.

Table 6.2 shows the PPH rates for both Centres. Further investigation by Centre showed some variance at all levels (≥500 ml 36.7% versus 27.4%; ≥1000 ml 10.2% versus 7.8%; ≥1500 ml 4.3% versus 3.3%) and is shown in Table 6.2a.

Table 6.2a: Overall incidence of estimated blood loss at different thresholds in each Centre, using ≥

Estimated blood Loss category	Centre 1	Centre 2	All
Geometric mean	395 (414 to 377)	305 (328 to 284)	349 (363 to 336)
Median (Quartiles)	400 (IQR 250 to 600)	300 (IQR 200 to 500)	350 (IQR 200 to 545)
No PPH	63.3% (60.1 to 66.4)	72.1% (67.8 to 76.0)	66.1% (63.5 to 68.6)
≥ 500 ml	36.7 % (33.6 to 39.9)	27.9% (24 to 32.2)	33.9 (31.4 to 36.5)
≥ 1000 ml	10.2% (9.0 to 11.4)	7.8% (6.4 to 9.4)	9.4% (8.5 to 10.4)
≥ 1500 ml	4.3% (3.5 to 5.2)	3.3% (2.6 to 4.3)	4.0% (3.4 to 4.6)
≥ 2000 ml	2.2% (1.7 to 2.9)	1.4% (1.0 to 1.9)	2.0% (1.6 to 2.4)
≥ 2500 ml	0.8% (0.6 to 1.1)	0.8% (0.6 to 1.2)	0.8% (0.7 to 1.0)

Postpartum haemorrhage, PPH.

Some authors report PPH as blood loss volumes exceeding thresholds. To assess incidence using these definitions, incidence of PPH in this cohort was calculated using >threshold volumes. Using these definitions the rates of PPH at all levels reduced; >500 ml= 25.6%; >1000 ml= 7.3%; >1500 ml= 3.1%; >2000 ml= 1.3%; >2500 ml= 0.6% (Table 4.2b). There was no significant difference in incidence between Centres.

Table 6.2b: Incidence of postpartum haemorrhage when estimated blood loss exceeded each threshold (>)

Estimated Blood Loss category	**Centre 1**	**Centre 2**	**All**
Geometric mean	395 (414 to 377)	305 (328 to 284)	349 (363 to 336)
Median (Quartiles)	400 (IQR 250 to 600)	300 (IQR 200 to 500)	350 (IQR 200 to 545)
Normal estimated blood loss	72.2% (69.3 to 74.8)	79.3% (75.7 to 82.6)	74.4% (72.2 to 76.6)
> 500 ml	27.8% (25.2 to 30.7)	20.7% (17.4 to 24.3)	25.6% (23.4 to 27.8)
> 1000 ml	7.9% (6.9 to 9.0)	6.1% (4.9 to 7.5)	7.3% (6.5 to 8.2)
> 1500 ml	3.3% (2.6 to 4.1)	2.6% (2.0 to 3.4)	3.1% (2.6 to 3.7)
> 2000 ml	1.4% (1.0 to 2.0)	1.0% (0.7 to 1.5)	1.3% (1.0 to 1.7)
> 2500 ml	0.6% (0.4 to 0.8)	0.7% (0.4 to 1.0)	0.6% (0.5 to 0.8)

Further analysis to ensure rates of severest haemorrhage (≥2500 ml) were not skewed by complexity of cases (referred to previously in Centre 1), showed rates of 0.82% versus 0.83% shown in Tables 6.2c and 6.2d. This compared with 0.56% (95% CI 0.49 to 0.62, n= 306/54910) in Scotland during the same period (Lennox C., 2011b).

Table 6.2c: Postpartum haemorrhage ≥2500 ml Centre 1

Blood loss category (ml)	Frequency	Percentage (%)	Cumulative	95% CI
<2500	6668	99.18	99.18	98.9 to 99.4
2500+	55	0.82	100.00	0.59 to 1.04

Table 6.2d: Postpartum haemorrhage ≥2500 ml Centre 2

Blood loss category (ml)	Frequency	Percentage	Cumulative	95% CI
<2500	3121	99.17	99.17	88.4 to 99.5
2500+	26	0.83	100.00	0.49 to 1.15

6.6 Effects of mode of delivery on estimated blood loss.

6.7

Tables 6.3a, b show estimated blood loss associated with mode of birth, in each Centre. Following SVD Centre 1 recorded higher rates of PPH ≥500 ml (18% vs 10%) and within this overall PPH rate higher estimated blood loss was reported at other thresholds (500-999 ml, 11% vs 6.9%; 1000-1499 ml, 2.7% vs 1.1%; ≥1500 ml, 3.3% vs 1.3). Conversely in Centre 2 instrumental birth was associated with almost twice the rate of PPH ≥500 ml than Centre 1 (44% vs 22.2%).

In Centre 1, emergency CS was associated with minimal blood loss <500 ml in almost 28% of cases, this was significantly less in Centre 2 where just under 10% did not experience PPH.

Table 6.3a: Estimated blood loss according to mode of birth in Centre 1

Mode of birth	**0-499 ml % (95%CI)**	**500- 999 ml % (95%CI)**	**1000-1499 ml % (95%CI)**	**≥ 1500 ml % (95%CI)**
SVD	82 (78.7 to 85)	11 (9.3 to 14.8)	2.7 (2.0 to 3.5)	3.3 (2.3 to 4.8)
Instrumental vaginal birth	56 (47.4 to 64.2)	30.2 (23.0 to 38.6)	8.3 (5.9 to 11.3)	5.3 (3.8 to 7.3)
Elective CS	36.1 (25.4 to 48.2)	52.4 (41.5 to 63.1)	8.0 (5.7 to 11,1)	3.5 (2.2 to 5.5)
Emergency CS	27.8 (20.9 to 35.9)	53.3 (46.3 to 60.2)	12.8 (10.3 to 15.7)	6.2 (4.7 to 8.2)

Table 6.3b: Estimated blood loss according to mode of birth in Centre 2

Mode of birth	0-499 ml % (95%CI)	500- 999 ml % (95%CI)	1000-1499 ml % (95%CI)	≥ 1500 ml % (95%CI)
SVD	90.8 (87.1 to 93.4)	6.9 (4.5 to 10.4)	1.1 (0.5 to 2.0)	1.3 (0.8 to 2.3)
Instrumental vaginal birth	63.8 (49.7 to 75.8)	28.6 (17.9 to 42.3)	3.7 (2.0 to 6.6)	3.9 (2.2 to 7.0)
Elective CS	39.8 (25.8 to 55.6)	48.1 (34.3 to 62.1)	8.3 (5.3 to 12.7)	3.9 (2.2 to 6.9)
Emergency CS	9.8 (3.3 to 25.7)	57.2 (45.5 to 68.2)	19.9 (13.5 to 28.4)	13.1 (8.8 to 19.1)

Table 6.3c shows estimated blood loss according to mode of birth in the study population (both Centres combined). Overall PPH ≥500 ml occurred following SVD in almost 15% or women, following instrumental vaginal birth in almost 42% of cases, following elective CS with almost 63% and after emergency CS in more than 75% of cases.

Table 6.3c: Estimated blood loss according to mode of birth in study population.

Mode of birth	0-499 ml % (95%CI)	500- 999 ml % (95%CI)	1000-1499 ml % (95%CI)	≥ 1500 ml % (95%CI)
SVD	85.2 (82.8 to 87.4)	10.0 (8.2 to 12.3)	2.1 (1.6 to 2.7)	2.7 (1.9 to 3.6)
Instrumental vaginal birth	58.3 (50.9 to 65.4)	29. 8 (23.6 to 36.8)	7.0 (5.3 to 9.3)	5.0 (3.8 to 6.5)
Elective CS	37.4 (28.7 to 47.0)	50.8 (42.2 to 59.4)	8.1 (6.2 to 10.5)	3.7 (2.5 to 5.2)
Emergency CS	23.9 (18.0 to 30.9)	54.1 (48.1 to 60.1)	14.3 (11.8 to 17.2)	7.7 (6.1 to 9.6)

Further comparison of estimation blood loss ≥ 1000 ml by mode of delivery showed the incidence following SVD was 4.75% (95%CI 0.37 to 5.7), after

vaginal instrumental delivery was 12.0% (95%CI 9.3 to 14.6), post elective CS was 11.8% (95%CI 8.9 to 14.5) and after emergency CS was 22% (95%CI 18.6 to 25.4).

Therefore, in the study cohort PPH ≥ 1000 ml following vaginal birth was 6.1% (95%CI 5.2 to 7.1) and following abdominal birth was 18.2% (95%CI 15.8 to 20.7).

Table 6.4 shows the number of case notes reviewed in each category according to estimated blood loss category and mode of birth.

Table 6.4: Notes reviewed according to estimated blood loss and mode of birth

Mode of birth	0-499 ml n	500- 999 ml n	1000-1499 ml n	≥ 1500 ml % n	Total N
SVD	507	103	103	113	826
Instrumental vaginal birth	74	75	86	68	303
Elective CS	34	84	80	36	234
Emergency CS	38	165	208	121	532
Total	**653**	**427**	**477**	**338**	**1895**

6.7 Effects of day and time of birth on presence and absence of PPH

Table 6.5a shows effects of day of the week and time of day of birth on incidence of PPH. These data are shown separately for women undergoing elective Caesarean birth due to the planned nature of the event (Table 6.5b). In those women with spontaneous, induced or augmented labour there was a marginal increase in babies born on Wednesday, Thursday and Friday. There were no

significant differences between no PPH and PPH ≥500 ml by day of the week or at any time of the day.

Table 6.5a: Days of the week and time of birth no postpartum haemorrhage (PPH) versus PPH ≥500 ml in women without elective Caesarean section.

	No PPH **n (%)**	**PPH≥500 ml** **n (%)**	**Total** **n**
n sampled	619	1042	1661*
n represented	6216	2735	8951*
Day of the week			
Sunday	816 (69.1)	365 (31.0)	1181
Monday	782 (68.0)	371 (32.1)	1153
Tuesday	712 (61.1)	453 (38.9)	1165
Wednesday	946 (68.1)	444 (31.9)	1390
Thursday	1025 (73.9)	361 (26.1)	1386
Friday	1035 (73.5)	373 (26.5)	1408
Saturday	900 (71.0)	368 (29.0)	1268
Time of delivery			
00.00- 02.59	781 (70.2)	332 (29.8)	1113
03.00- 05.59	879 (73.1)	324 (26.9)	1203
06.00- 08.59	815 (73.3)	297 (26.7)	1112
09.00- 11.59	748 (63.9)	422 (36.1)	1170
12.00- 14.59	796 (69.9)	343 (30.1)	1139
15.00- 17.59	777 (67.4)	376 (32.6)	1153
18.00-20.59	666 (68.6)	305 (31.4)	971
21.00- 23.59	754 (69.2)	336 (30.8)	1090

*women undergoing elective Caesarean birth are excluded from this analysis

Table 6.5b shows slightly more babies were born by elective CS on Wednesday, with significantly fewer on Friday and, unsurprisingly, on Saturday or Sunday. Table 6.5b shows the majority of these elective procedures occurred between 09.00-17.59 hours, with women undergoing the procedure between 09.00-11.59

hours at greatest risk of PPH ≥500 ml (35.3% vs 0.1%). Interestingly 2% of these elective procedures occurred between 21.00- 08.59 hours, which would not generally be considered appropriate for elective procedures.

Table 6.5b: Days of the week and time of birth, no postpartum haemorrhage (PPH) versus PPH ≥500 ml for women with elective Caesarean section.

	No PPH **n (%)**	**PPH≥500 ml** **n (%)**	**Total**
n sampled	35	201	236
n represented	369	617	986
Days of the week			
Sunday	0 (0%)	3 (100)	3
Monday	48 (28.6)	120 (71.4)	168
Tuesday	61 (30.8)	137 (69.2)	198
Wednesday	92 (37.7)	152 (62.3)	244
Thursday	84 (37.3)	141 (62.3)	225
Friday	48 (49.5)	49 (50.5)	97
Saturday	36 (70.6)	15 (29.4)	51
Time of birth (h)			
00.00-0.2.59	0 (0)	1 (100)	1
03.00- 05.59	0 (0)	6 (100)	6
06.00- 08.59	0 (0)	6 (100)	6
09.00- 11.59	188 (46.1)	220 (53.9)	408
12.00- 14.59	121 (40.1)	181 (59.9)	302
15.00- 17.59	36 (19.4)	150 (80.6)	186
18.00- 20.59	24 (31.6)	52 (68.4)	76
21.00- 23.59	0 (0)	1 (100)	1

6.8 Comparison with historic data

Comparison with severe PPH (≥1500 ml) data collected in the units providing maternity care in the same geographical locations in 1997-1998 reveals a 19.7% increase in birth rate (8,329 to 10,213) and 3.4 (95% CI 2.7 to 4.3) risk ratio for PPH ≥1500 ml from 1.12% (95% CI 0.92 to 1.38) to 4.20% (93 cases versus 391) and an 8.3 (95% CI 4.0 to 17.1) risk ratio for PPH ≥2500 ml (9 cases versus 81) (Waterstone *et al*., 2001).

6.9 PPH incidence at thresholds commonly used in research and audit reports

Tables 6.6a-d show the number of women sampled (n) and the number of women represented (nw) with % incidence of estimated blood loss at the various thresholds. Values within the variable were also investigated, for example, mean age for blood loss thresholds, number of antenatal day unit attendances (0-5+), parity (0-3+) and number of previous PPHs.

6.9.1 Maternal demographic characteristics and estimated blood loss category.

Table 6.6a shows there is a trend for increased age to be associated with increased estimated blood loss, but the effect is modified by extremes of age in each blood loss category. The majority of women in each ethnic group did not have a PPH (≥500 ml), the exception being Chinese women with 46.3% losing <500 ml, this may have been influenced by the small numbers of this ethnicity

within the cohort (0.6%). The % of women in each estimated blood loss category did not differ by index of multiple deprivation (IMD) classification.

Table 6.6a: Population characteristics and estimated blood loss at different thresholds.

Risk factor	**Estimated Blood Loss category (ml)**					**All**
	25-499	500-999	1000-1499	1500-1999	2000+	
n sampled	653	427	477	167	171	1895
n represented	6585	2419	542	198	193	9937
Demography						
Mean Age at delivery (years)	**30.0 (6.1)**	**31.5 (5.8)**	**31.2 (5.5)**	**31.6 (5.4)**	**31.7 (5.8)**	**30.5 (6.0)**
<20	77.7%	17.1%	2.4%	1.2%	1.7%	100%
20-24	77.9%	14.9%	4.4%	1.5%	1.3%	100%
25-29	66.6%	24.7%	5.0%	2.0%	1.7%	100%
30-34	63.2%	26.7%	6.5%	1.8%	1.7%	100%
35-39	63.3%	25.8%	5.4%	2.9%	2.6%	100%
40+	57.7%	32.1%	6.0%	1.8%	2.5%	100%
Ethnicity						
White	68.5%	23.8%	4.5%	1.7%	1.6%	100%
Black	59.9%	26.7%	8.0%	2.5%	2.8%	100%
Asian	65.6%	24.5%	5.2%	3.0%	1.8%	100%
Mixed/other	68.9%	21.5%	5.6%	2.0%	1.9%	100%
Ethnicity detail						
White	68.5%	23.8%	4.5%	1.7%	1.6%	100%
Black British	82.0%	9.8%	4.1%	2.6%	1.6%	100%
Black Caribbean	67.4%	26.8%	3.7%	0.7%	1.4%	100%
Black African	55.5%	28.7%	9.5%	3.0%	3.3%	100%
Bangladeshi	78.8%	17.7%	1.8%	0.6%	1.2%	100%
Indian	60.5%	27.8%	5.2%	4.9%	1.5%	100%
Pakistani	65.0%	23.5%	6.7%	2.7%	2.2%	100%
Other Asian	60.8%	30.4%	15.9%	4.8%	2.4%	100%
Chinese	46.3%	30.5%	15.9%	4.9%	2.4%	100%
Mixed	78.4%	16.9%	3.5%	1.2%	3.7%	100%
Other/unknown	67.6%	22.5%	4.9%	1.3%	3.7%	100%
ii) Local deprivation (Index of multiple deprivation & subscales; based on area of residence)						
Index of multiple deprivation (IMD)	28.3 (13.2)	28.2 (12.8)	29.6 (12.0)	28.0 (12.2)	29.8 (12.7)	28.4 (13.0)
Most deprived UK quintile (20%)	65.9%	23.7%	6.1%	2.0%	2.2%	100%
Less deprived UK quintile (80%)	66.6%	24.6%	5.1%	2.0%	1.8%	100%
Barriers to housing & services	31.0 (8.9)	31.9 (8.8)	32.8 (8.8)	31.5 (8.1)	33.1 (9.7)	31.3 (8.9)
Most deprived UK quintile (%)	63.8%	25.7%	6.2%	2.1%	2.2%	100%
Less deprived UK quintile (80%)	70.3%	22.2%	4.3%	1.8%	1.5%	100%
Crime & disorder	0.6 (0.7)	0.6 (0.7)	0.6 (0.6)	0.6 (0.7)	0.6 (0.7)	0.6 (0.7)
Most deprived UK quintile (%)	66.2%	24.9%	5.1%	2.0%	1.8%	100%
Less deprived UK quintile (80%)	66.4%	23.8%	5.8%	2.0%	2.0%	100%

Education, skills & training	19.2 (11.9)	17.1 (10.2)	19.0 (10.7)	20.0 (12.8)	17.8 (11.9)	18.7 (11.5)
Most deprived UK quintile	77.5%	13.6%	5.0%	2.3%	1.7%	100%
Less deprived UK quintiles (80%)	65.2%	25.4%	5.5%	1.9%	2.0%	100%
Employment	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (01)	0.1 (0.1)
Most deprived UK quintile (%)	68.2%	21.2%	6.9%	1.5%	2.2%	100%
Less deprived UK quintiles (80%)	65.7%	25.3%	5.0%	2.1%	1.9%	100%
Health, deprivation & disability	0.2 (0.7)	0.2 (0.7)	0.3 (0.6)	0.2 (0.6)	0.2 (0.7)	0.2 (0.7)
Most deprived UK quintile	66.5%	24.4%	5.5%	1.4%	2.2%	100%
Less deprived UK quintile (80%)	66.3	24.2%	5.5%	2.1%	1.9%	100%
Income	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Most deprived UK quintile (%)	66.2%	23.6%	6.2%	2.0%	1.9%	100%
Less deprived UK quintile (80%)	66.5%	24.7%	5.0%	2.0%	2.0%	100%
Living environment	35.5 (18.1)	37.4 (17.4)	38.2 (16.7)	37.1 (18.0)	39.2 (18.0)	36.2 (17.9)
Most deprived UK quintile (%)	64.4%	25.5%	6.0%	2.0%	2.1%	100%
Less deprived UK quintile (80%)	68.9%	22.6%	4.7%	2.0%	1.8%	100%

6.9.2 General health and pre-index pregnancy characteristics and estimated blood loss category

Table 6.6b shows the general health and pre-index pregnancy characteristics association with estimated blood loss at all thresholds. Women with higher BMIs in the overweight (BMI 25.1 to 30 kg/m^2) and obese (BMI 30.1 to 35 kg/m^2) classifications were more likely to have excessive blood loss defined as estimated blood loss exceeding 500 ml than those with a low BMI (<19 kg/m^2). There was no difference in estimated blood loss categories for women whose BMI was in the normal range (19.1-25 kg/m^2). There were fewer cigarette smokers at first antenatal appointment in the higher estimated blood loss categories.

Most pre-existing maternal conditions in the study population were representative of the incidence in the general population, and were not associated with excessive blood loss. This was especially apparent in women with Lupus, although the numbers of women with this condition in the population were small despite Centre 1 being the regional referral hospital for this condition. The exceptions to these findings were the presence of uterine fibroids and female circumcision, whose association with PPH have been reported previously (WHO, 2012a; Cook *et al*., 2010). Additionally, women with pre-existing hypertension and clotting/thrombotic disorders were also likely to experience PPH ≥500 ml. Women on treatment for depression or receiving oral iron supplementation for anaemia at first antenatal appointment were less likely to experience PPH ≥500 ml.

Table 6.6b: Estimated blood loss following childbirth by general and pre-pregnancy health

Risk factor	**Blood loss category (ml)**					**All**
	25-499	500-999	1000-1499	1500-1999	2000+	
n sampled	652	427	477	167	171	1895
n represented	6585	2419	542	198	193	9937
iii) General health and pre-index pregnancy risk factors						
Mean maternal height (cm)	164.5 (6.8)	164.4 (7.1)	164.7 (7.3)	163.3 (6.8)	165.7 (6.8)	164.5 (6.9)
Mean maternal weight (Kg)	67.3 (14.7)	67.2 (14.3)	71.3 (18.4)	72.2. (14.1)	70.5 (15.6)	67.6 (14.9)
Mean BMI (Kg/m^2)	24.9 (5.2)	24.8 (5.0)	26.2 (5.9)	27.1 (5.3)	25.7 (5.6)	25.0 (5.2)
BMI<19	71.9%	23.0%	3.8%	0.5%	0.7%	100%
BMI 19-25	66.1%	25.6%	4.9%	1.5%	1.9%	100%
BMI 25.1-30	66.2%	23.0%	6.4%	2.1%	2.2%	100%
BMI 30.1- 35	62.9%	23.8%	6.1%	4.8%	2.4%	100%
35.1+	62.7%	22.1%	9.0%	3.2%	3.0	100%
Current smoker	71.9%	23.7%	2.8%	0.6%	1.0%	100%
Non-smoker	65.5%	24.4%	5.8%	2.2%	2.1%	100%
Lupus	80.0%	0.0%	20.0%	0.0%	0.0%	100%
No Lupus	66.2%	24.4%	5.4%	2.0%	2.0%	100%
Pre-gestational Diabetes	59.4%	29.7%	5.9%	3.0%	2.0%	100%
No pre-existing diabetes	66.3%	24.3%	5.5%	2.0%	1.9%	100%
Epilepsy (on treatment)	52.2%	39.1%	2.2%	6.5%	0.0%	100%
No epilepsy	66.33%	24.3%	5.5%	2.0%	1.9%	100%
Depression (on treatment)	71.1%	24.2%	2.3%	1.2%	1.2%	100%

No depression	66.1%	24.4%	5.5%	2.0%	1.9%	100%
Anaemia (on iron at booking)	71.4%	17.9%	5.9%	3.6%	1.2%	100%
No anaemia at booking (Hb≥11 g/l)	66.2%	24.4%	5.5%	2.0%	1.9%	100%
Pre-existing hypertension	48.0%	36.0%	13.0%	0.0%	3.0%	100%
No pre-existing hypertension	66.5%	24.2%	5.4%	2.0%	1.9%	100%
Fibroids	55.1%	29.7%	10.0%	3.1%	2.2%	100%
No fibroids	66.8%	24.1%	5.2%	1.9%	1.9%	100%
FGM	62.5%	25.1%	5.2%	3.1%	4.1%	100%
No FGM	66.4%	24.3%	5.5%	2.0%	1.9%	100%
Clotting/ thrombotic disorders	38.1%	43.3%	11.3%	3.1%	4.1%	100%
No clotting/thrombotic disorders	66.5%	24.2%	5.4%	2.0%	1.9%	100%
Uterine anomaly	57.1%	28.6%	9.5%	0.0%	4.8%	100%
No uterine anomaly	66.3%	24.3%	5.5%	2.0%	1.9%	100%
Previous obstetric history						
Previous PPH	56.4%	29.6%	4.9%	5.7%	3.5%	100%
No previous PPH	66.7%	24.1%	5.5%	1.8%	1.9%	100%
Number of previous PPH						
0	66.7%	24.1%	5.5%	1.8%	1.9%	100%
1	58.2%	27.7%	5.1%	4.9%	3.6%	100%
2	0.0%	66.7%	0.0%	33.3%	0.0%	100%
3	0.0%	85.7%	0.0%	14.3%	0.0%	100%
Previous CS	44.4%	41.8%	8.4%	2.4%	3.2%	100%
No previous CS	69.8%	21.6%	5.0%	1.9%	1.7%	100%
Para 0	61.1%	28.5%	6.3%	2.0%	2.0%	100%
Para 1	71.3%	20.5%	4.9%	1.5%	1.8%	100%
Para 2	71.7%	19.5%	4.2%	3.2%	1.5%	100%
Para 3+	72.8%	19.4%	3.7%	1.6%	2.4%	100%
Multiparity	71.6%	20.1%	4.5%	2.0%	1.8%	100%
Primiparity	61.1%	28.5%	6.3%	2.0%	2.1%	100%

Female genital mutilation, FGM; postpartum haemorrhage, PPH; Caesarean section, CS.

In those with a previous obstetric history, these data show women with a previous PPH or CS were more likely to experience PPH ≥500 ml concurring with others (Sinha and Mishra, 2012; Ford *et al*., 2007). Primiparous women were more likely not to experience PPH ≥500 ml than the multiparous women.

6.9.3 Index pregnancy events and health and impact on estimated blood loss category

Table 6.6c shows that women experiencing multiple pregnancy, assisted conception to achieve current pregnancy, antenatal admission, antenatal day unit attendance (irrespective of reason for admission/attendance), non –specific symptoms of feeling generally unwell, pre-eclampsia screen, confirmed (and treated) UTI and bleeding per vagina (not requiring admission) were more likely to experience PPH ≥500 ml. There was no apparent trend for increased estimated blood loss relating to abdominal pain, external cephalic version, itching (symptom of obstetric cholestasis), suspected spontaneous rupture of fetal membranes (ROM), growth scan (suspected intrauterine growth restriction or macrosomia), chest pain/ shortness of breath, suspected UTI or feeling faint/dizzy.

Table 6.6c: Percentage of women affected, according current pregnancy health and events, in detail, and estimated blood loss at different thresholds

Risk factor	**Estimated Blood Loss category (ml)**					**All**
	25-499	500-999	1000-1499	1500-1999	2000+	
n sampled	653	427	477	167	171	1895
n represented	6585	2419	542	198	193	9937
v) Current pregnancy						
Singleton pregnancy	66.8%	24.1%	5.4%	1.9%	1.9%	100%
Multiple pregnancy	47.6%	34.3%	8.7%	4.7%	4.7%	100%
Number of fetuses = 2 (twins)	49.2%	32.9%	8.9%	4.5%	4.5%	100%
Number of fetuses = 3+	0.0%	75.0%	0.0%	12.5%	12.5%	100%
Assisted conception for current pregnancy	34.7%	45.6%	9.7%	6.5%	3.6%	100%
No assisted conception for current pregnancy	67.5%	23.4%	5.2%	2.0%	1.8%	100%
Antenatal admissions (inpatient nights)	59.6%	29.2%	6.6%	2.2%	2.5%	100%
No antenatal admissions (inpatient nights)	66.3%	23.4%	5.2%	2.0%	1.8%	100%

Admissions <24/40	73.3%	14.6%	7.3%	2.4%	2.4%	100%
No admissions <24/40	66.2%	24.5%	5.4%	2.0%	1.9%	100%
Admissions >24/40	57.4%	31,3%	6.5%	2.3%	2.5%	100%
No admissions >24/40	67.8%	23.2%	5.3%	2.0%	1.9%	100%
Any ADU attendance	63.4%	26.0%	5.8%	2.5%	2.3%	100%
No ADU attendances	69.1%	22.7%	5.2%	1.5%	1.6%	100%
Number of ADU attendances:						
ADU attendance 1	65.2%	24.5%	5.5%	2.4%	2.5%	100%
ADU attendance 2	58.5%	30.7%	6.4%	2.6%	1.8%	100%
ADU attendance 3	62.0%	25.2%	6.7%	3.8%	2.2%	100%
ADU attendance 4	84.5%	8.5%	4.2%	1.4%	1.4%	100%
ADU attendance 5	0.0%	66.7%	11.1%	11.1%	11.1%	100%
Abdominal pain	64.2%	26.8%	4.9%	1.9%	2.2%	100%
No abdominal pain	66.7%	23.9%	5.6%	2.0%	1.9%	100%
Itching	63.8%	24.8%	6.7%	2.9%	1.9%	100%
No itching	66.3%	24.3%	5.4%	2.0%	1.9%	100%
Fainting/dizziness	63.5%	21.2%	9.4%	4.1%	1.8%	100%
No fainting/dizziness	66.3%	24.4%	5.4%	2.0%	1.9%	100%
IM iron	0.0%	0.0%	100%	0.0%	0.0%	100%
No IM iron	66.3%	24.4%	5.5%	2.0%	1.9%	100%
ECV	57.9%	33.1%	5.5%	1.4%	2.1%	100%
No ECV	66.4%	24.2%	5.5%	2.0%	1.9%	100%
PE Screen	55.7%	31.3%	8.0%	2.2%	2.7%	100%
No PET screen	67.2%	23.7%	5.2%	2.0%	1.9%	100%
CTG (antenatal)	52.3%	37.5%	6.2%	1.2%	1.8%	100%
No CTG (antenatal)	66.7%	23.9%	5.4%	2.0%	1.9%	100%
Growth scan	82.8%	6.9%	6.9%	1.2%	2.3%	100%
No growth scan	66.1%	24.5%	5.4%	2.0%	1.9%	100%
Reduced fetal movements	63.6%	26.0%	5.6%	3.3%	1.7%	100%
No reduced fetal movements	66.7%	24.1%	5.4%	1.8%	2.0%	100%
Possible ROM	64.0%	25.6%	55.4%	2.7%	2.4%	100%
No attendance for suspected ROM	66.64	24.2%	5.5%	1.9%	1.9%	100%
Generally unwell	61.6%	20.1%	8.8%	6.4%	3.1%	100%
No attendance for feeling generally unwell	66.4%	24.5%	5.3%	1.8%	1.9%	100%
Possible UTI	0.0%	50%	50%	0.0%	0.0%	100%
No suspicion of UTI	66.3%	24.3%	5.4%	2.0%	1.9%	100%
Severe headaches	0.0%	100%	0.0%	0.0%	0.0%	0.1%
No severe headaches	66.3%	24.3%	5.5%	2.0%	1.9%	100%
PV bleed - not requiring admission	66.5%	22.3%	5.2%	3.4%	2.6%	100%
No PV bleed- not requiring admission	66.3%	24.4%	5.5%	1.9%	1.9%	100%

Chest pain/ shortness of breath	74.4%	20.4%	1.4%	1.9%	1.9%	100%
No chest pain or shortness of breath	66.1%	24.4%	5.5%	2.0%	1.9%	100%
Placenta praevia						
Placenta praevia	20.0%	31.7%	15.0%	5.0%	28.3%	100%
No placenta Praevia	66.5%	24.3%	5.4%	2.0%	1.8%	100%
Major placenta praevia	0.0%	41.9%	22.6%	0.0%	35.5%	100%
No major placenta praevia	66.5%	24.3%	5.4%	2.0%	1.8%	100%
Minor placenta praevia	42.9%	21.4%	7.1%	10.7%	17.9%	100%
No minor placenta praevia	66.3%	24.4%	5.5%	2.0%	1.9%	100%
Anterior placenta praevia	0.0%	0.0%	35.3%	5.9%	58.8%	100%
No anterior placenta praevia	66.3%	24.4%	5.4%	2.0%	1.9%	100%
Posterior placenta praevia	28.6%	45.2%	7.1%	4.8%	14.3%	100%
No posterior placenta praevia	66.4%	24.3%	5.5%	2.0%	1.9%	100%
APH	59.3%	23.9%	8.1%	2.6%	6.0%	100%
No APH	66.5%	24.4%	5.4%	1.9%	1.8%	100%
Gestation of APH ≤ 24/40	45.3%	47.2%	1.9%	1.9%	3.8%	100%
Gestation of APH >24/40	61.6%	20.1%	9.2%	2.7%	6.4%	100%
UTI (confirmed)	64.0%	24.9%	6.0%	2.4%	2.7%	100%
No UTI	66.4%	24.3%	5.4%	2.0%	1.9%	100%
Number of UTI =1	64%	25.0%	5.9%	2.4%	2.8%	100%
Number of UTI =2	66.2%	24.3%	6.8%	1.4%	1.4%	100%
Number of UTI =3	0.0%	0.0%	0.0%	100%	0.0%	100%
Gestational hypertension	46.6%	40%	8.3%	1.4%	3.8%	100%
No gestational hypertension	66.8%	23.9%	5.4%	2.0%	1.9%	100%
Pre-eclampsia	29.9%	51.5%	11.3%	2.5%	4.9%	100%
No Pre-eclampsia	67%	23.9%	5.3%	2.0%	1.9%	100%
Pre-eclampsia <34 weeks	23.1%	48.1%	21.2%	3.9%	3.9%	100%
No Pre-eclampsia <34 weeks'	66.5%	24.2%	5.4%	2.0%	1.9%	100%
Pre-eclampsia 34+ weeks'	32.2%	52.6%	7.9%	2.0%	5.3%	100%
No pre-eclampsia 34^{+} weeks'	66.8%	23.9%	5.4%	2.0%	1.9%	100%
Anaemia Hb <10.5 g/ml)	63.3%	24.7%	6.7%	3.2%	2.2%	100%
No anaemia <10.5 g/ml	66.7%	24.4%	5.3%	1.8%	1.9%	100%
Anaemia (Hb <11.1 g/ml)	30.3%	29.8%	32.7%	38.4%	26.9%	30.4%
No anaemia <11.1 g/ml	66.0%	23.9%	5.9%	2.5%	1.7%	100%

Antenatal day unit, ADU; intramuscular, IM; external cephalic version, ECV; pre-eclampsia, PET; cardiotocograph, CTG; rupture of membranes, ROM; urinary tract infection, UTI; per vagina, PV; antepartum haemorrhage, APH.

The incidence of severe haemorrhage defined as EBL exceeding 1500 ml was higher in women with placenta praevia. Women who had an antepartum haemorrhage (APH) >24 weeks' were more likely to experience greater estimated blood loss (Table 4.4c). Women with pre-eclampsia and anaemia (Hb <11.1 g/l in third trimester, but prior to onset of labour) were also more likely to experience PPH ≥500 ml. There were no trends for greater estimated blood loss in women who had vaginal bleeding in early pregnancy (prior to 24 weeks' gestation).

6.9.4 Intrapartum events and management and estimated blood loss category

Table 6.6d shows that more women who had induced and augmented onset of labour experienced estimated blood loss over 500 ml. There appeared to be a linear trend between raised maternal temperature in labour and higher categories of estimated blood loss. This was the single most missing data point in the reviewed notes. Therefore this analysis was undertaken with all available data, and then repeated treating missing as 'unknown'. In both analyses maternal pyrexia was associated with increased estimated blood loss (Table 6.6d). Evidence of chorioamnionitis was also associated with PPH ≥500 ml.

Table 6.6d: Percentage of women affected, according intrapartum, birth and third stage management factors, and estimated blood loss at different thresholds.

Risk factor	Estimated Blood loss category (ml)					All
	0-499	500-999	1000-1499	1500-1999	2000+	
n sampled	653	427	477	167	171	1895
n represented	6585	2419	542	198	193	9937
Group 7: intrapartum and delivery						
Onset of labour spontaneous	74.1%	18.6%	4.2%	1.6%	1.5%	100%
Induced	59.1%	27.7%	7.9%	2.8%	2.5%	100%
Augmented	58.4%	29.2%	5.4%	2.9%	4.1%	100%
No labour onset	35.1%	50.1%	9.1%	2.9%	2.8%	100%
Highest temperature in labour ≥37.0°C treating missing as unknown	48.3%	34.9%	9.9%	3.8%	3.2%	100%
Highest temperature in labour <37.2°C treating missing as unknown	68.9%	22.9%	4.8%	1.7%	1.8%	100%
Highest temperature in labour ≥37.5°C treating missing as unknown	32.7%	44.2%	12.6%	6.2%	4.3%	100%
Highest temperature in labour <37.5°C treating missing as unknown	67.6%	23.6%	5.2%	1.8%	1.9%	100%
Highest temperature in labour 37.8°C treating unknown as NO	21.4%	46.9%	17.9%	9.3%	4.6%	100%
Highest temperature in labour <37.8°C treating missing as unknown	67.1%	24.0%	5.25	1.9%	1.9%	100%
Highest temperature in labour 38.0°C treating missing as unknown	1.6%	51.6%	18.8%	20.3%	7.8%	100%
Highest temperature in labour <38.0°C treating missing as unknown	66.7%	24.2%	5.4%	1.9%	1.9%	100%
Duration of ruptured membranes (days)	0.4 (0.7)	0.6 (0.7)	0.6 (0.8)	0.7 (0.9)	0.6 (0.7)	0.5 (0.7)
Duration of ROM (days)= 0	71.8%	20.2%	4.7%	1.8%	1.5%	100%
Duration of ROM (days)= 1	60.3%	27.0%	5.6%	2.7%	4.4%	100%
Duration of ROM (days)= 2+	56.9%	31.5%	6.9%	2.8%	1.9%	100%
Dinoprostone	58.7%	29.3%	6.8%	2.7%	2.5%	100%

No dnoprostone	67.6%	23.5%	5.2%	1.9%	1.8%	100%
Dinoprostone dose	0.2 (0.6)	0.3 (0.8)	0.4 (1.0)	0.5 (1.3)	0.3 (0.9)	0.2 (0.7)
Dinoprostone = 1	60.7%	28.7%	6.3%	2.1%	2.3%	100%
Dinprostone = 2+	54.5%	30.5%	7.8%	4.1%	3.1%	100%
Oxytocin (Syntocinon®) during $1^{st}/2^{nd}$ stage	50.1%	34.6%	9.5%	3.0%	2.9%	100%
No Oxytocin (Syntocinon®) during $1^{st}/2^{nd}$ stage of labour	71.5%	21.1%	4.2%	1.7%	1.6%	100%
Mode of delivery-SVD	85.2%	10.0%	2.1%	1.3%	1.4%	100%
Operative vaginal delivery	58.3%	29.8%	7.0%	2.5%	2.5%	100%
ElCS	37.5%	50.8%	8.0%	1.9%	1.7%	100%
EmCS	23.9%	54.1%	14.3%	4.1%	3.7%	100%
Physiological 3^{rd} stage	84.1%	13.8%	0.7%	1.1%	0.3%	100%
Active management of third stage of labour	64.9%	25.2%	5.8%	2.1%	2.1%	100%
Oxytocin (Syntocinon®) IM (3^{rd} stage)*	72.9	14.0%	7.4%	1.8%	3.9%	6.7%
No Oxytocin (Syntocinon ®) IM (3^{rd} stage)	65.8%	25.1%	5.3%	2.0%	1.8%	100%
Oxytocin (Syntocinon®) IV*	31.1%	51.2%	11.5%	3.3%	3.0%	100%
No Oxytocin (Syntocinon®) IV	80.3%	13.7%	3.1%	1.5%	1.5%	100%
Ergometrine Maleate/Oxytocin (Syntometrine®) IM*	81.6%	12.8%	2.8%	1.5%	1.4%	100%
No Ergometrine/Maleate (Syntometrine®) IM	46.2%	39.4%	9.0%	2.7%	2.7%	100%
Oxytocin (Syntocinon®) infusion increased*	63.7%	25.5%	7.2%	1.7%	1.9%	100%
No Oxytocin (Syntocinon®) infusion increased	66.5%	24.3%	5.3%	2.0%	1.9%	100%
Oxytocin (Syntocinon®) 40/50 IU commenced*	37.3%	47.2%	9.7%	2.9%	2.9%	100%
No Oxytocin (Syntocinon®) 40/50 IU commenced	79.0%	14.3%	3.6%	1.6%	1.5%	100%
Retained placenta	37.0%	36.2%	14.5%	6.0%	6.4%	100%
No retained placenta	67.0%	24.1%	5.2%	1.9%	1.8%	100%
Evidence of chorioamnionitis	0.0%	41.2%	17.7%	23.5%	17.7%	100%
No evidence of chorioamnionitis	66.4%	24.3%	5.4%	2.0%	1.9%	100%

Rupture of membranes, ROM; international units IU; intramuscular, IM; intravenous, IV. * Routine prophylactic treatment as part of active management of third stage of labour.

All modes of delivery, apart from spontaneous vaginal birth, were associated with increased estimated blood loss categories. Eighty four per cent of women who had physiological management of the third stage of labour did not have excessive blood loss (<500 ml). All prophylactic uterotonics were associated with blood loss in all categories, with fewer women experiencing higher levels of estimated blood loss having received Ergometrine Maleate/Oxytocin (Syntometrine®) compared to those who received oxytocin (Syntocinon®); the exception being when oxytocin (Syntocinon®) is administered in a 40/50 IU infusion (Table 6.6d).

6.9.5 Influence of place of birth and estimated blood loss category

Forty percent of women giving birth in obstetric units experienced PPH ≥500 ml. The relationship between mode of delivery and place of birth should be considered in this result. The largest blood losses (2000+ ml) occurred in the hospital birth Centres, but the incidence of PPH 1500-1999 ml was highest following homebirths.

Table 6.6e: Place of birth and incidence of blood loss at various levels

Risk factor	Estimated blood loss category (ml)					All
	25-499	500-999	1000-1499	1500-1999	2000+	
n sampled	651	427	477	167	171	1893
n represented	6583	2419	542	198	193	9935
Place of birth						
Hospital	60.7%	28.1%	6.6%	2.3%	2.4%	100%
Midwife-led unit	85.8%	11.5%	1.6%	0.7%	0.5%	100%
Home	91.0%	4.9%	0.8%	3.3%	0.0%	100%
Other*	91.4%	6.5%	0.0%	2.2%	0.0%	100%

*Births not attended by midwives or doctors. All but one occurred outside hospital or midwife led unit, the majority were at home, but due to the unattended nature of the birth, these were analysed separately from planned or unplanned homebirths with a midwife present.

6.10 Summary

The sample selection was appropriate and representative of the population from which it was drawn. There were, however, differences between this and the general UK population, particularly in terms of ethnicity and age. Incidence of pre-existing diseases was generally lower than reported elsewhere, the exceptions being ethnicity related (uterine fibroids and female genital mutilation). There were more primiparous women than reported elsewhere, which may reflect the inner city population served by Centre 1.

Many factors previously identified as associated with PPH≥500 ml were confirmed, including: increasing maternal age (Cameron *et al.,* 2006) primiparity (Gilbert *et al.*, 1987), previous CS (Coulter-Smith *et al.*, 1996), multiple pregnancy (Sebire *et al.,* 2001), placenta praevia (Oyelese and Smullian, 2006), fibroids (Jolley, 2009), female genital mutilation (Banks *et al.*, 2006), induction of labour, elective and emergency CS, oxytocin (Syntocinon®) IV and retained placenta. The association with PPH ≥500 ml and Black African ethnicity, assisted conception techniques, gestational hypertension, pre-eclampsia and temperature in labour require further validation. Factors associated with EBL<500 ml included: multiparity, smoking at first antenatal contact, SVD, physiological management of the third stage of labour, prophylactic intramuscular Syntometrine® and, to a lesser degree, oxytocin (Syntocinon®).

My study reports the highest rates of PPH at all thresholds, except >2500 ml, when the rate is comparable to contemporaneous data (Lennox C., 2011a). Intrapartum factors appeared to have the greatest impact on estimated blood loss, with all interventions conferring increased association with PPH. Some, such

CS, were associated with minor haemorrhage but not progression to more severe levels of estimated blood loss. The linear trend in increased estimated blood loss associated with maternal temperature is new and may be associated with evidence of chorioamnionitis, which was also associated with PPH.

There was no difference in PPH incidence by day of the week or time of day for any mode of birth. Giving birth in obstetric units was associated with higher levels of estimated blood loss, concurring with the findings of others (Hollowell *et al*., 2011). But complexity of cases and birth mode must be considered here. These results demonstrate the initial impact of factors whilst highlighting the complexity around risk factors for PPH at all levels. It is apparent that more analyses are required to further investigate the influences of individual and combinations of factors, these are presented in Chapter 7.

Chapter 7: Results 2; Selection of variables prediction of PPH for use in regression models.

Regression analysis facilitates statistical estimation of the relationships among variables. More precisely, it enables calculation of the impact of an independent variable on a dependent variable, in this case, estimated blood loss, whilst all other independent variables remain fixed (Field, 2009). Multiple regression analysis is employed when there are several potential predictors, as in this case. Table 7.5 a, b and c identifies the influence of independent variables on estimated blood loss (mean ml) and independent predictors for PPH ≥500 ml in each of the three groups (A. Pre-pregnancy, B. Current pregnancy and C. Labour and birth).

7.2 Reference group selection

A reference group is a group that other groups or individuals are compared to (Coggan, 2003). The purpose of a reference group is for comparison with the characteristics of another group or individual. Thus reference groups in this work were selected following discussion with the Stop Study Advisory Group and statistician. It was decided that groups considered "normal" (for example BMI 19-24.9 kg/m^2) or most common (for example, White ethnicity) would be the reference group. Reference groups are described in Table 7.1.

Table 7.1: Reference groups and rationale for their use in this study

Variable	Reference group	Reason for using this as reference group
Age	20-24 years	Reported as ideal time for childbirth.
Ethnicity	White	Major ethnic group (60%)
BMI	19- 24.9 kg/m^2	"normal" BMI range.
Parity	0 (primiparous women)	Multiparity is reported to confer protection.
Onset of labour	spontaneous	"normal" no intervention.
Duration of ruptured membranes (ROM)	1 hour	Commonly ROM precedes labour, usually by at least an hour.
ProsinE_2®	0 (none)	Spontaneous labour with no interventions considered normal.
Mode of birth	Spontaneous vaginal delivery (SVD)	"normal" no intervention.

7.3 Factors and their influence on mean estimated blood loss

Factors not significantly associated with increased mean estimated blood loss included: maternal age <20 years; maternal ethnicity- Black British, Black Caribbean, Bangladeshi, Indian, Pakistani, Asian (other than Chinese); all categories of BMI; all but one category assessing index of multiple deprivation; pre-existing maternal diseases- diabetes, epilepsy, depression, lupus, anaemia, essential hypertension female genital mutilation and gestation at booking.

Table 7.2a shows pre-pregnancy factors that appear to be independently significantly associated with increased mean estimated blood loss. These included maternal age (67 ml for each 10 years, 95% CI 38 to 97 ml) in addition to a linear increase with age groups: 25-29 years 78 ml (23 to 133 ml), 30-34 years 102 ml (48 to 157 ml), 35-39 years 115 ml (54 to 176 ml), ≥40 years 123 ml (31 to 215 ml). Ethnicities associated with increased mean estimated blood loss:

Black African 128 ml, (64 to 192 ml), Chinese 237 ml (34 to 441 ml) and unknown 90 ml (1 to 180 ml). One aspect of the Index of multiple deprivation (IMD)- barriers to housing and services was associated with estimated increased mean blood loss of 61 ml (22 to 100 ml). Whilst the impact of BMI (1 to 10 ml) for each unit of BMI, would appear modest at first glance, the cumulative affect on the obese and morbidly obese should not be underestimated.

The only significant pre-existing medical condition associated with increased mean estimated blood loss was uterine fibroids 116 ml (4 to 229 ml). Assisted conception techniques were also associated with increased mean estimated blood loss, 234 ml (108 to 360 ml). Previous PPH and CS were associated with increased mean estimated blood loss 164 ml (7 to 284 ml) and 194 (116 to 271 ml) respectively.

Variables associated with reduced mean estimated blood loss were associated with some ethnicities, most apparent in those of mixed race, -96ml (-174 to -19 ml). Other variables associated with reduced mean estimated blood loss included current cigarette smoking, -82 ml (-141 to -21); BMI<19 kg/m^2, -93 ml (-152 to -34 ml) and multiparity -80 ml (-118 to -42 ml); para 1, -73ml (-119 to -27 ml); para 2, -96 ml (-150 to -41 ml); para 3+, -82 ml (-118 to -42 ml).

Table 7.2a: Changes in estimated blood loss in Group A: Pre-pregnancy and principal predictors of postpartum haemorrhage (PPH) ≥500 ml

	ml (range)	**Odds Ratio (OR) (95% CI)**
Variable	**Mean change in EBL (ml)**	**≥500 ml All women**
Group A: Pre-pregnancy		
i) Age		
Age for each 10 years	67 (38 to 97)	**1.46 (1.21 to 1.77)**
Age in years		
20- 24 years reference group		
<20 years	-17 (-99 to 65)	1.01 (0.51 to 2.00)
25 – 29 years	78 (22 to 133)	**1.79 (1.20 to 2.68)**
30 – 34 years	103 (48 to 158)	**2.03 (1.39 to 2.96)**
35 – 39 years	115 (54 to 176)	**2.00 (1.33 to 3.01)**
≥40 years	123 (31 to 215)	**2.54 (1.44 to 4.48)**
Ethnicity		
White (reference group)		
Black British	-53 (-152 to 46)	0.46 (0.20 to 1.06)
Black Caribbean	-48 (-125 to 29)	1.01 (0.57 to 1.78)
Black African	128 (64 to 192)	**1.68 (1.23 to 2.28)**
Bangladeshi	-78 (-170 to 14)	0.56 (0.22 to 1.46)
Indian	117 (-33 to 267)	1.40 (0.73 to 2.67)
Pakistani	45 (-39 to 128)	1.13 (0.62 to 2.04)
Chinese	237 (34 to 441)	2.54 (0.73 to 8.82)
Other Asian	88 (-175 to 351)	1.35 (0.38 to 4.75)
Mixed	-96 (-174 to -19)	0.59 (0.26 to 1.33)
Other/unknown	90 (1 to 180)	1.01 (0.60 to 1.71)
ii) Local deprivation		
IMD*: most deprived quintile	4 (-35 to 43)	1.00 (0.80 to 1.26)
Barriers to housing & services	61 (22 to 100)	**1.29 (1.02 to 1.62)**
Crime & disorder	-1 (-51 to 25)	1.00 (0.80 to 1.25)
Education, skills & training	-63 (-126 to 0)	**0.57 (0.39 to 0.85)**
Employment	-9 (-50 to 32)	0.88 (0.68 to 1.14)
Health, deprivation & disability	-5 (-51 to 41)	0.97 (0.72 to 1.30)
Income	4 (-34 to 43)	0.99 (0.78 to 1.24)
Living environment	29 (-9 to 68)	1.18 (0.94 to 1.48)
iii) General and pre-existing health risk factors		
Current smoker	-82 (-142 to -22)	0.74 (0.51 to 1.07)
BMI per unit (kg/m^2)	6 (1 to 10)	1.01 (0.99 to 1.04)
BMI detail		
19.0 – 25.0 reference group		
<19	-93 (-152 to -34)	0.74 (0.45 to 1.23)
25.1 – 30.0	24 (-25 to 74)	1.00 (0.75 to 1.33)
30.1 – 35.0	51 (-21 to 124)	1.14 (0.79 to 1.66)
≥35.1	97 (-26 to 220)	1.15 (0.67 to 1.97)
Lupus	-101 (-442 to 238)	0.48 (0.05 to 4.61)
Diabetes	34 (-121 to 189)	1.31 (0.41 to 4.26)
Epilepsy (on treatment)	46 (-120 to 212)	1.76 (0.33 to 9.46)
Depression (on treatment)	-49 (-128 to 29)	0.80 (0.39 to 1.62)

Anaemia (iron at first appointment	6 (-151 to 163)	0.76 (0.24 to 2.43)
Essential hypertension	172 (-73 to 418)	2.09 (0.67 to 6.56)
Uterine fibroids	116 (3 to 229)	1.60 (0.94 to 2.70)
FGM	75 (-31 to 181)	1.15 (0.61 to 2.19)
Clotting/ thrombotic disorders	189 (-32 to 411)	3.14 (0.91 to 10.90)
Uterine anomaly	-26 (-365 to 312)	1.44 (0.13 to 15.66)
Planned pregnancy	36 (-6 to 78)	1.06 (0.82 to 1.38)
Assisted conception	234 (107 to 360)	**3.80 (1.69 to 8.57)**
Gestation at booking	-0 (-3 to 3)	1.00 (0.98 to 1.01)
iv) Obstetric history		
Previous PPH	164 (7 to 320)	1.52 (0.86 to 2.68)
>1 previous PPH	153 (22 to 284)	1.62 (0.99 to 2.64)
Previous CS	195 (118 to 273)	**2.80 (2.00 to 3.94)**
Parity (using 0 as reference range)		
1	-73 (-119 to -27)	**0.64 (0.49 to 0.83)**
2	-96 (-150 to -41)	**0.62 (0.44 to 0.89)**
3+	-77 (-161 to -7)	**0.58 (0.37 to 0.91)**
Multiparity	-80 (-118 to -42)	**0.62 (0.50 to 0.78)**

For continuous measures (e.g. age, BMI) the change is given for each additional 10 years of age or 1kg/m^2 of BMI. For variables with more than 2 categories (e.g. ethnicity) a reference group is declared (White), and comparisons are made to this. * Index of multiple deprivation & subscales based on area of residence, UK, IMD; estimated blood loss, EBL; female genital mutilation, FGM.

Independent factors arising during pregnancy and not significantly associated with increased mean estimated blood loss included: any antenatal admissions; elevated systolic or diastolic blood pressure at booking; abdominal pain; itching; fainting; external cephalic version; cardiotocography (CTG); growth scan; reduced fetal movements; possible spontaneous rupture of membranes (SROM); possible or confirmed urinary tract infection; antenatal day unit attendance for APH (no admission); chest pain/shortness of breath; anaemia (<11.0 g/l and <10.5 g/l); polyhydramnios; medications in pregnancy- anti allergy, anti eclampsia, antidepressants, antiemetics, asthma treatments, diabetic medication (oral and insulin), oral iron, steroids for maternal reasons, tocolytics and thyroxine. There was insufficient evidence to assess the effect of ursodeoxycholic acid (URSO) (given to women with obstetric cholestasis to ease pruritus).

Table 7.2b shows pregnancy events and health associated with increased mean estimated blood loss included: multiple pregnancy, 208 ml (90 to 326 ml), antenatal admissions >24 weeks gestation, 54 ml (0 to 107 ml); any antenatal day unit attendance 49 ml (11 to 87 ml); IM iron 512 ml (493 to 531 ml); pre-eclampsia screen 81ml (12 to 150 ml); "generally unwell" (no diagnosis) 132 ml (13 to 251 ml); severe headaches 262 ml (243 to 281 ml).

All placenta praevia was associated with increased mean estimated blood loss, 1270 ml (410 to 2130 ml) anterior placenta praevia increased mean estimated blood loss by 2909 ml (1150 to 4669 ml). APH was associated with increased mean blood loss, 172 ml (15 to 329 ml) but "warning APH" (defined as recurrent, heavy, red) was associated with greater increased mean estimated blood loss 1145 ml (325 to 1965 ml).

Also associated with increased mean estimated blood loss was gestational hypertension 131 ml (11 to 252 ml), pre-eclampsia (all) 219 ml (113 to 326 ml), <34 weeks' gestation 235 ml (17 to 452 ml), >34 weeks' gestation 212 ml (92 to 333 ml). Medications in the last week of pregnancy associated with increased mean estimated blood loss included, antibiotics 52 ml (5 to 98 ml), antihypertensives 105 ml (927 to 182 ml), aspirin 129 ml (14 to 244 ml), blood thinners 174 ml (19 to 330 ml), steroids for fetal reasons 106 ml (12 to 201 ml) and pain relief 154 ml (27 to 281 ml).

Table 7.2b: Changes in estimated blood loss in group B: Current pregnancy, and principal predictors of postpartum haemorrhage ≥500 ml.

	ml (range)	**Odds Ratio (OR) (95% CI)**
Variable	**Mean change in EBL (ml)**	**≥500ml All women**
Group B: Pregnancy v) Current pregnancy		
Multiple pregnancy	208 (90 to 326)	**2.15 (1.05 to 4.41)**
Number of fetuses	215 (100 to 330)	**2.18 (1.11 to 4.29)**
Antenatal admissions (any)	42 (-10 to 94)	**1.37 (1.01 to 1.87)**
Admissions >24/40	54 (0 to 107)	**1.52 (1.10 to 2.09)**
sBP at booking	10 (-7 to 27)	1.04 (0.95 to 1.15)
Booking sBP≥140 mmHg	234 (-42 to 510)	3.06 (0.87 to 10.75)
Booking sBP ≥160 mmHg	788 (-415 to 1991)	$
dBP at booking (for each 10 mmHg)	19 (-7 to 45)	1.07 (0.94 to 1.22)
Booking dBP ≧90mmHg	115 (-145 to 374)	1.31 (0.45 to 3.83)
Booking dBP ≧100mmHg	1345 (-334 to 3024)	$
vi) Antenatal day Unit (ADU)		
Any ADU attendance	49 (11 to 87)	**1.28 (1.02 to 1.60)**
>1 ADU attendance	27 (6 to 49)	**1.15 (1.01 to 1.31)**
Abdominal pain	11 (-35 to 57)	1.10 (0.81 to 1.50)
Itching	39 (-76 to 155)	1.13 (0.54 to 2.40)
Fainting/ dizziness	39 (-89 to 167)	1.10 (0.48 to 2.51)
IM iron	512 (493 to 531)	*
ECV	143 (-4 to 291)	1.40 (0.55 to 3.56)
Pre-eclampsia screen	81 (12 to 150)	**1.62 (1.07 to 2.43)**
CTG	43 (-54 to 140)	1.78 (0.94 to 3.36)
Growth scan	33 (-190 to 256)	0.40 (0.12 to 1.31)
Reduced fetal movements	4 (-54 to 62)	1.14 (0.82 to 1.59)
Possible ROM	18 (-37 to 72)	1.12 (0.81 to 1.56)
'Generally unwell' (no diagnosis)	132 (13 to 251)	1.22 (0.66 to 2.23)
Possible UTI	262 (-85 to 610)	$
Severe headaches	262 (243 to 281)	$
ADU for APH (no admission)	53 (-56 to 163)	0.99 (0.56 to 1.74)
Chest pain/ shortness of breath	-71 (-174 to 32)	0.67 (0.28 to 1.58)
vii) Placenta praevia		
Placenta praevia	1270 (410 to 2130)	**7.74 (1.02 to 58.41)**
Major placenta praevia	1931 (525 to 3336)	NA
Minor placenta praevia	477 (-41 to 996)	2.56 (0.30 to 21.59)
Anterior placenta praevia	2909 (1150 to 4669)	NA
Posterior placenta praevia	564 (61 to 1068)	4.81 (0.59 to 38.89)
vii) APH and UTI		
APH	172 (15 to 329)	1.36 (0.78 to 2.37)
"Warning" APH	1145 (325 to 1965)	7.26 (0.96 to 55.16)
UTI	20 (-41 to 80)	1.08 (0.73 to 1.60)
> 1 UTI	16 (-37 to 69)	1.07 (0.76 to 1.58)
ix) Pre-eclampsia and anaemia		
Gestational hypertension	131 (11 to 252)	**2.29 (1.15 to 4.54)**

Pre-eclampsia (all)	219 (113 to 326)	**4.63 (1.79 to 11.96)**
Pre-eclampsia <34/40	235 (17 to 452)	6.44 (0.81 to 51.41)
Pre-eclampsia >34/40	212 (92 to 333)	**4.12 (1.41 to 11.98)**
Anaemia<10.5 g/ml	40 (-20 to 101)	1.15 (0.83 to 1.60)
Anaemia <11.1 g/ml	5 (-39 to 50)	1.00 (0.79 to 1.28)
Polyhydramnios	75 (-178 to 328)	0.29 (0.03 to 2.90)
x) Medications pre-delivery (in the week prior to birth)		
Allergy medications	141 (-63 to 346)	2.37 (0.78 to 7.16)
Anti-eclampsia meds	165 (-114 to 444)	1.00 (0.19 to 5.25)
Antibiotics	52 (5 to 98)	**1.35 (1.02 to 1.80)**
Antidepressants/mood disorders	12 (-107 to 131)	1.01 (0.48 to 2.09)
Antiemetics	-61 (-124 to 1)	0.74 (0.51 to 1.08)
Antihypertensives (including for pre-eclampsia)	105 (27 to 182)	**1.76 (1.11 to 2.78)**
Aspirin	129 (14 to 244)	1.50 (0.81 to 2.81)
Asthma medications	93 (-18 to 204)	1.71 (0.88 to 3.29)
Blood thinners	174 (19 to 330)	1.58 (0.83 to 3.01)
Medication for diabetes	100 (-44 to 244)	**2.62 (1.04 to 6.57)**
Steroids for fetal reasons	106 (12 to 201)	1.17 (0.77 to 1.79)
Oral iron	23 (-25 to 70)	1.08 (0.82 to 1.44)
Steroids for maternal reasons	53 (-65 to 170)	1.17 (0.59 to 2.33)
Pain relief	154 (27 to 281)	1.62 (0.73 to 3.58)
Threatened preterm birth	246 (-220 to 712)	1.77 (0.59 to 5.31)
Thyroid disease	241 (-99 to 581)	1.55 (0.65 to 3.71)
URSO	$	$

Estimated blood loss, EBL; systolic blood pressure, sBP; diastolic blood pressure, dBP; antenatal day unit, ADU; imtramuscular, IM; external cephalic version, ECV; cardiotocograph, CTG; rupture of membranes, ROM; urinary tract infection, UTI; antepartum haemorrhage, APH; ursodeoxycholic acid, URSO; not applicable, NA; all women had EBL ≥500ml; numbers too small, $.

The association between independent labour and birth factors with mean blood loss and PPH ≥500 ml are shown in Table 7.2c. Independent labour and birth factors not significantly associated with increased mean estimated blood loss included gestational age at birth, administration of one dose of dinoprostone, duration of oxytocin (Syntocinon®) and unknown maternal temperature in labour. Third stage variables which failed to be significantly associated with increased mean estimated blood loss included oxytocin (Syntocinon®) IM, oxytocin (Syntocinon®) infusion increased and unknown interval to suturing of genital tract trauma.

Independent significantly associated labour and birth factors included maximum birth weight 50 ml (15 to 85 ml), total birth weight 69 ml (38 to 101 ml), macrosomia >4 kg 128 ml (55 to 201 ml) and >4.5 kg 156 ml (31 to 281 ml). Induced and augmented labours were associated with 100 ml (50 to 150 ml) and 113 ml (14 to 211 ml) respectively. Also associated with increased mean estimated blood loss were epidural analgesia 159 ml (117 to 202 ml), spinal anaesthesia 181 m (137 to 226 ml), temperature in labour >37.2°C suggested a linear trend with each increasing degree of temperature, and oxytocin (Syntocinon®) use in first and/or second stage of labour 137 ml (92 to 183 ml).

Vaginal instrumental births (ventouse or forceps) were associated with increased mean estimated blood loss of 194 ml (132 to 255 ml), elective CS by 298 ml (238 to 358 ml) and emergency CS by 409 ml (357 to 461 ml). Active management of the third stage utilising oxytocin (Syntocinon®) IV bolus, as prophylactic uterotonic, was associated with an increase in estimated mean blood loss by 317 ml (276 to 359 ml) and oxytocin (Syntocinon®) 40/50 IU by 273 ml (232 to 313 ml).

Intrapartum independent variables associated with reduced mean estimated blood loss were: physiological third stage of labour -177 ml (-223 to -130 ml) and Ergometrine Maleate/Oxytocin (Syntometrine®) IM -234 ml (-272 to -196 ml).

Table 7.2c: Changes in estimated blood loss in group C: Labour and birth, and principal predictors of PPH ≥500 ml.

	ml (range)	**Odds Ratio (OR) (95% CI)**
Variable	**Mean change in EBL (ml)**	**≥500 ml All women**
Group C: Labour and birth		
xi) Gestation at birth		
Gestational age at birth	0 (-9 to 9)	1.03 (0.98 to 1.09)
xii) Birth weight		
Maximum birth weight* (kg)	50 (15 to 85)	**1.50 (1.22 to 1.85)**
Total birth weight (kg)*	69 (38 to 101)	**1.55 (1.27 to 1.89)**
Macrosomia >4 kg	128 (55 to 201)	**1.94 (1.33 to 2.82)**
Macrosomia >4.5kg	156 (31 to 281)	**2.96 (1.19 to 7.36)**
xii) Onset of labour		
Spontaneous onset (reference group)		
Augmented	113 (14 to 211)	**1.96 (1.19 to 3.24)**
Induced	100 (50 to 150)	**1.90 (1.39 to 2.60)**
None (prelabour CS)	262 (202 to 323)	**5.07 (3.41 to 7.53)**
Duration of ROM (days)	65 (28 to 102)	**1.55 (1.20 to 1.99)**
Duration of ROM (hours)		
< 1 h (reference group)		
1-2 h	34 (-53 to 121)	1.16 (0.66 to 2.02)
2-3 h	147 (45 to 249)	**2.48 (1.40 to 4.40)**
3-6 h	78 (24 to 131)	**1.76 (1.12 to 2.76)**
6-12 h	192 (135 to 250)	**4.44 (2.91 to 6.78)**
12-24 h	253 (187 to 319)	**6.33 (4.06 to 9.86)**
24+ h	198 (123 to 274)	**4.23 (2.68 to 6.67)**
No ROM/ROM at CS	326 (259 to 392)	**10.99 (6.70 to 18.04)**
Unknown ROM duration	280 (219 to 341)	**6.39 (4.28 to 9.54)**
Dinoprostone	54 (5 to 104)	**1.43 (1.04 to 1.96)**
Dinoprostone 0 (reference group)		
Dinoprostone x 1	27 (-29 to 84)	1.32 (0.91 to 1.92)
Dinoprostone x 2+	112 (26 to 199)	**1.69 (1.00 to 2.87)**
xiv) Intrapartum		
Oxytocin (Syntocinon ®)	137 (92 to 183)	**2.40 (1.84 to 3.14)**
Duration of oxytocin (Syntocinon®)	10 (0 to 19)	**1.06 (1.00 to 1.13)**
Spinal anaesthesia	181 (137 to 226)	**4.10 (2.93 to 5.75)**
Epidural analgesia	159 (117 to 202)	**2.91 (2.22 to 3.81)**
Temperature >37.2°C	190 (127 to 252)	**2.65 (1.86 to 3.77)**
Temperature >37.5°C	282 (169 to 396)	**4.60 (2.34 to 9.06)**
Temperature >37.8°C	413 (234 to 592)	**7.94 (2.48 to 25.43)**
Temperature >38.0°C	724 (368 to 1080)	**132.72 (17.53 to 1004.68)**
Temperature unknown	41 (-2 to 84)	**1.28 (1.00 to 1.65)**
Evidence of chorioamnionitis	796 (261 to 1330)	NA
xv) Birth		
Mode of birth- SVD (reference group)		
Instrumental vaginal birth	194 (132 to 255)	**3.84 (2.71 to 5.44)**
Elective CS	298 (238 to 358)	**8.95 (5.80 to 13.79)**

Emergency CS	409 (357 to 461)	**17.05 (11.47 to 25.34)**
xvi) third stage		
Physiological third stage	-177 (-223 to -130)	**0.47 (0.30 to 0.75)**
Oxytocin (Syntocinon® IM)	18 (-71 to 106)	0.70 (0.44 to 1.11)
Oxytocin (Syntocinon®) IV (bolus)	317 (276 to 359)	**8.56 (6.42 to 11.41)**
Ergometrine maleate/Oxytocin (Syntometrine®) IM	-234 (-272 to -196)	**0.19 (0.15 to 0.25)**
Oxytocin (Syntocinon®) IV increased	36 (-23 to 94)	1.10 (0.71 to 1.69)
Oxytocin (Syntocinon®) 40/50 IU infusion commenced	273 (232 to 313)	**6.07 (4.64 to 7.92)**
Retained placenta	374 (154 to 594)	**3.49 (1.55 to 7.82)**
Interval to suturing	113 (14 to 212)	0.97 (0.81 to 1.16)
Unknown interval to suturing	65 (-3 to 133)	**1.69 (1.05 to 2.72)**

For variables with more than 2 categories (e.g. onset of labour) a reference group is declared (spontaneous), and comparisons are made to this. Not applicable NA; all women had EBL ≥500 ml; Caesarean section, CS; rupture of membranes, ROM; spontaneous vaginal delivery, SVD; intramuscular, IM; intravenous, IV. *maximum birth weight= weight of singleton baby, or heaviest baby in multiple pregnancy; total birth weight= weight of singleton, or combined birth weights of twins, triplets and quadruplets.

7.4 Variables associated with PPH ≥500 ml

With reference to Tables 7.2 a, b and c the odds ratios (OR) for PPH ≥500 ml were calculated. Effect size varied considerably, with the highest risk factors occurring closest to birth, as described below.

7.4.1 Group A Pre-pregnancy associations with PPH ≥500 ml

Independent significant factors for increased mean estimated blood loss that failed to reach significance for PPH ≥500 ml were: Chinese ethnicity (OR 2.54, 95% CI 0.73 to 8.82]) and unknown ethnicity (OR 1.01, 95% CI 0.60 to 1.71). Mixed ethnicity which was associated with reduced mean estimated blood loss

was also not significant when applied to PPH ≥500 ml (OR 0.59, 95% CI 0.26 to 1.33) a similar effect was seen with smoking (OR 0.74, 95% CI 0.51 to 1.07), BMI (OR 1.01, 95% CI 0.99 to 1.04), uterine fibroids (OR 1.60, 95% CI 0.94 to 2.70) and previous PPH (OR 1.52, 95% CI 0.86 to 2.68).

Conversely IMD category 'education skills and training' whilst not significantly associated with increased mean estimated blood loss (OR -63 ml, 95% CI -126 to 0 ml) was associated with reduced PPH≥500 ml (OR 0.57, 95% CI 0.39 to 0.85). Maternal age per 10 years was associated with increased risk of PPH ≥500 ml (OR 1.46, 95% CI 1.21 to 1.77). Further investigation showed a small incremental effect size with maternal age (25- 29 years OR 1.79, 95% CI 1.20 to 2.68, to 40+ years OR 2.54, 95% CI 1.44 to 4.48). Other pre-pregnancy factors associated with a modest increased risk of PPH ≥500 ml were women of Black African ethnicity (OR 1.68, 95% CI 1.23 to 2.28) and in one component of the IMD (barriers to housing & services) (OR 1.29, 95% CI 1.02 to 1.62).

Assisted conception (OR 3.80, 95% CI 1.69 to 8.57) and previous CS (both elective and emergency) (OR 2.80, 95% CI 2.00 to 3.94) conveyed moderate risk of PPH. Only multiparity (OR 0.62, 95% CI 0.50 to 0.78) was protective against PPH ≥500 ml.

7.4.2 Group B Current pregnancy factors associated with PPH ≥ 500 ml

Factors that failed to be significant for increased estimated mean blood loss, but are significantly associated with PPH ≥500 ml include: antenatal admissions (OR 1.37 95% CI 1.01 to 1.87), 'generally unwell' (OR 1.22, 95% CI 0.66 to 2.23); pre-eclampsia <34 weeks' (OR 6.44, 95% CI 0.81 to 51.41); APH (OR 1.36, 95% CI 0.78 to 2.37), 'warning' APH (OR 7.26, 95% CI 0.96 to 55.16). Medications in the week preceding labour which also failed to be significantly associated with PPH ≥500 ml but were associated with increased mean estimated blood loss included; aspirin (OR 1.50, 95% CI 0.81 to 2.81), blood thinners (OR 1.58, 95% CI 0.83 to 3.01), steroids for fetal reasons (OR 1.17, 95% CI 0.77 to 1.79) and pain relief (OR 1.62, 95% CI 0.73 to 3.58).

Current pregnancy factors with a small effect on PPH ≥500 ml (Table 5.2b) included: antenatal day unit attendance (any reason) (OR 1.28, 95% CI 1.02 to 1.60); antenatal admission >24 weeks' gestation (defined as at least 1 night antenatal inpatient stay: for any reason) (OR 1.52, 95% CI 1.10 to 2.09); pre-eclampsia screen (serial BP/urinalysis/full blood screen/growth scan) (OR 1.62, 95% CI 1.07 to 2.43). Medications in the week preceding birth associated with PPH were antibiotics (OR 1.35, 95% CI 1.02 to 1.80), antihypertensives (for gestational hypertension and pre-eclampsia) (OR 1.62, 95% CI 1.07 to 2.43).

Factors with a moderate size effect on incidence of PPH ≥500 ml were multiple pregnancy (OR 2.15 95% CI 1.05 to 4.41); gestational hypertension (OR 2.29, 95% CI 1.15 to 4.54) and diabetes medication in last week of pregnancy (both for pre-existing and gestational diabetes) (OR 2.62, 95% CI 1.04 to 6.59).

The largest size effects influenced by current pregnancy health and events were diagnosis of pre-eclampsia (all) (OR 4.63, 95% CI 1.79 to 11.96) and after 34 weeks' gestation (OR 4.12, 95% CI 1.41 to 11.98) and placenta praevia, all degrees and positions (OR 7.74, 95% CI 1.02 to 58.41), women with anterior and major praevia all bled >500 ml).

7.4.3 Group C Intrapartum, birth and third stage factors associated with PPH ≥500 ml

Interval to suturing, although associated with increased mean estimated blood loss, was not significantly associated with PPH ≥500 ml (OR 0.97, 95% CI 0.81 to 1.16).

Labour and birth predictors of PPH ≥500 ml (Table 5.2c) in order of effect size were: maximum birthweight (weight of heaviest infant) (OR 1.50, 95% CI 1.22 to 1.85) total birth weight (combined weights of infants in multiple pregnancies) (OR 1.55, 95% CI 1.27 to 1.89); macrosomia (incrementally with birth weight >4 kg and >4.5 kg) (OR 1.94, 95% CI 1.33 to 2.82 and OR 2.96, 95% CI 1.19 to 7.36); induction of labour (OR 1.90, 95% CI 1.39 to 2.60); dinoprostone pessaries/gel (OR 1.43, 95% CI 1.04 to 1.96); two or more dinoprostone pessaries (or doses of gel) (OR 1.69, 95% CI 1.00 to 2.87); augmentation of the first and/or second stage of labour (OR 1.96, 95% CI 1.19 to 3.24) and duration of oxytocin (Syntocinon®) during first or second stage of labour (OR 1.06, 95% CI 1.00 to 1.13).

Moderate size effects were seen following the use of oxytocin (Syntocinon®) in the first and/or second stage of labour (OR 2.40, 95% CI 1.84 to 3.14); use of epidural analgesia (OR 2.91, 95% CI 2.22 to 3.81); duration of ROM, 2-3 hours (OR 2.48, 95% CI 1.40 to 4.40); instrumental vaginal birth (OR 3.84, 95% CI 2.71 to 5.44) and retained placenta (OR 3.49, 95% CI 1.55 to 7.82).

Large effect size was seen with; duration of ruptured membranes (ROM) 12-24 hours (OR 6.33, 95% CI 4.06 to 9.86) spinal anaesthesia (OR 4.10, 95% CI 2.93 to 5.75); temperature in labour >37.5°C (OR 4.60, 95% CI 2.34 to 9.06), >37.8°C (OR 7.94, 95% CI 2.48 to 25.43), >38.0°C (OR 132.72, 95% CI 17.53 to 1004.68).

Evidence of chorioamnionitis was always associated with PPH ≥500 ml.

Elective and emergency CS were both associated with PPH ≥500 ml (OR 8.95, 95% CI 5.80 to 13.79 and OR 17.05, 95% CI 11.47 to 25.34 respectively). Third stage management associated with increased risk of PPH ≥500 ml included oxytocin (Syntocinon®) IV bolus (OR 8.56, 95% CI 6.42 to 11.41) and 40/50 IU infusion (OR 6.07, 95% CI 4.64 to 7.92). Conversely Ergometrine Maleate/Oxytocin (Syntometrine®) IM was associated with reduced risk of PPH ≥500 ml (OR 0.19, 95% CI 0.15 to 0.25) as was physiological management of the third stage of labour (OR 0.47, 95% CI 0.30 to 0.75).

7.5 Factors associated with PPH ≥1000 ml and ≥1500 ml

Further regression analyses were undertaken on a reduced dataset of all women who lost ≥500 ml (n= 1302) to ascertain the factors associated with PPH progression to ≥1000 ml and ≥1500 ml which could be considered more clinically important. In these analyses the association between individual variables and PPH ≥1000 ml and ≥ 1500 ml are investigated.

7.5.1 Pre-pregnancy factors associated with PPH ≥1000 ml and ≥1500 ml

Table 7.3a shows significant pre-pregnancy factors associated with PPH ≥1000 ml, although not progression to ≥1500 ml were: Black African ethnicity (OR 1.52, 95% CI 1.09 to 2.12); BMI 25.1-30 (OR 1.44, 95% CI 1.04 to 2.00) and BMI ≥35.1 (OR 2.02, 95% CI 1.11 to 3.68) and planned pregnancy (OR 1.36, 95% CI 1.01 to 1.84).

Pre-pregnancy factors associated with PPH ≥1000 ml and ≥1500 ml and shown in Table 7.3a included: IMD education, skills and training, (OR 1.92, 95% CI 1.13 to 3.26 and OR 1.98, 95% CI 1.18 to 3.32); BMI per unit (OR 1.05, 95% CI 1.02 to 1.08 and OR 1.04 95% CI 1.01 to 1.07) and BMI 30.1-35.0 (OR 1.66, 95% CI 1.07 to 2.57 and OR 1.95, 95% CI 1.16 to 3.29).

Pre-pregnancy factors associated with PPH ≥1500 ml but not with lesser estimated blood loss were: previous PPH (OR 2.40, 95% CI 1.27 to 4.54) and >1 previous PPH (OR 2.40, 95% CI 1.36 to 4.23), para 2 (those expecting their third child) (OR 1.73, 95% CI 1.04 to 2.88). Conversely essential hypertension was negatively associated with PPH ≥1500ml (OR 0.27, 95%CI 0.08 to 0.97). These data are also shown in Table 7.3a.

Table 7.3a: Pre-pregnancy variables associated with postpartum haemorrhage (PPH) ≥1000 ml and ≥1500 ml.

Variable	Odds Ratio (OR) (95% CI)	
	≥1000 ml (women with PPH ≥ 500 ml)	**≥1500 ml (women with PPH ≥500 ml)**
Group A: Pre-pregnancy		
i) Age		
Age for each 10 years	0.94 (0.75 to 1.17)	0.97 (0.76 to 1.25)
Age at delivery in years		
20-24 years reference range		
<20 years	0.64 (0.27 to 1.52)	0.99 (0.41 to 2.40)
25-29 years	0.76 (0.46 to 1.28)	0.92 (0.53 to 1.61)
30-34 years	0.78 (0.48 to 1.29)	0.75 (0.43 to 1.30)
35-39 years	0.84 (0.49 to 1.42)	1.06 (0.58 to 1.93)
40+ years	0.64 (0.34 to 1.19)	0.70 (0.35 to 1.37
Ethnicity		
White (reference group)		
Black British	2.31 (0.70 to 7.65)	2.01 (0.69 to 5.84)
Black Caribbean	0.60 (0.32 to 1.11)	0.47 (0.21 to 1.03)
Black African	**1.52 (1.09 to 2.12)**	1.13 (0.76 to 1.69)
Bangladeshi	0.55 (0.17 to 1.82)	0.62 (0.15 to 2.52)
Indian	1.21 (0.50 to 2.90)	1.44 (0.45 to 4.64)
Pakistani	1.36 (0.67 to 2.76)	1.09 (0.45 to 2.64)
Chinese	2.20 (0.76 to 6.31)	1.25 (0.46 to 3.41)
Other Asian	0.80 (0.23 to 2.77)	0.73 (0.17 to 3.04)
Mixed	0.83 (0.30 to 2.26)	0.52 (0.15 to 1.76)
Other/unknown	1.23 (0.69 to 2.18)	1.27 (0.70 to 2.30)
ii) Local deprivation		
IMD* most deprived	1.14 (0.87 to 1.49)	0.96 (0.69 to 1.34)
Barriers to housing & services	1.07 (0.82 to 1.40)	0.87 (0.64 to 1.20)
Crime and disorder	0.85 (0.65 to 1.11)	0.88 (0.64 to 1.22)
Education, skills & training	**1.92 (1.13 to 3.26)**	**1.98 (1.18 to 3.32)**
Employment	1.35 (1.00 to 1.83)	0.94 (0.68 to 1.29)
Health, deprivation & disability	0.90 (0.66 to1.24)	0.80 (0.56 to 1.15)
Income	1.11 (0.85 to 1.46)	0.87 (0.63 to 1.20)

Living environment	0.95 (0.73 to 1.24)	0.76 (0.56 to 1.05)
iii) General & medical risk factors		
Current smoker	**0.47 (0.31 to 0.71)**	**0.48 (0.29 to 0.80)**
BMI per unit (kg/m^2)	**1.05 (1.02 to 1.08)**	**1.04 (1.01 to 1.07)**
BMI detail		
19.0 - 25.0 reference group		
<19.0	0.63 (0.35 to 1.13)	**0.34 (0.15 to 0.81)**
25.1 - 30.0	**1.44 (1.04 to 2.00)**	1.33 (0.92 to 1.92)
30.1 – 35.0	**1.66 (1.07 to 2.57)**	**1.95 (1.16 to 3.29)**
35.1+	**2.02 (1.11 to 3.68)**	1.62 (0.92 to 2.88)
Lupus	$	$
Diabetes	0.89 (0.27 to 2.96)	0.91 (0.26 to 3.17)
Epilepsy (on treatment)	0.54 (0.12 to 2.42)	1,04 (0.22 to 4.99)
Depression (on treatment)	0.54 (0.24 to 1.22)	0.77 (0.31 to 1.89)
Anaemia (iron at first appointment)	1.46 (0.39 to 5.45)	1.31 (0.35 to 4.95)
Essential hypertension	1.08 (0.42 to 2.80)	**0.27 (0.08 to 0.97)**
Uterine fibroids	1.27 (0.76 to 2.14)	0.62 (0.35 to 1.11)
FGM	1.21 (0.62 to 2.34)	1.72 (0.86 to 3.41)
Clotting/ thrombotic disorders	1.04 (0.36 to 3.05)	0.76 (0.19 to 3.00)
Uterine anomaly	1.22 (0.13 to 11.76)	0.60 (0.05 to 6.67)
Planned pregnancy	**1.36 (1.01 to 1.84)**	1.08 (0.73 to 1.60)
Assisted conception	1.08 (0.58 to 2.01)	1.32 (0.57 to 3.07)
Gestation at booking	1.00 (0.98 to 1.02)	0.98 (0.95 to 1.00)
iv) Obstetric history		
Previous PPH	1.19 (0.67 to 2.11)	**2.40 (1.27 to 4.54)**
>1 previous PPH	1.09 (0.68 to 1.73)	**2.40 (1.36 to 4.23)**
Previous CS	0.77 (0.56 to 1.06)	0.76 (0.47 to 1.22)
Parity (using 0 as reference group)		
1	1.13 (0.82 to 1.55)	1.11 (0.74 to 1.68)
2	1.26 (0.82 to 1.92)	**1.73 (1.04 to 2.88)**
3+	1.05 (0.61 to 1.81)	1.50 (0.75 to 3.03)
Multiparity	1.15 (0.88 to 1.50)	1.31 (0.93 to 1.86)

For continuous measures (e.g. age, BMI) the change is given for each additional 10 years of age or 1 kg/m^2 of BMI. For variables with more than 2 categories (e.g. ethnicity) a reference group is declared (White), and comparisons are made to this. Index of multiple deprivation & subscales based on area of residence, UK, IMD; numbers too small, $; female genital mutilation, FGM; Caesarean section, CS.

7.5.2 Current pregnancy health and events associated with PPH ≥1000 ml and PPH ≥1500 ml.

All results are shown in Table 7.3b, and summarised here.

There were no pregnancy related/acquired variables associated with PPH progression to ≥1000 ml although not to ≥1500 ml.

Current pregnancy health variables associated with progression to both ≥1000 ml and ≥1500 ml included attendance at ADU feeling "generally unwell" with no definitive diagnosis (OR 2.33, 95% CI 1.13 to 4.81 and OR 2.30, 95% CI 1.09 to 4.88); placenta praevia (all) (OR 3.80, 95% CI 1.21 to 11.93 and OR 4.86, 95% CI 1.99 to 11.87); APH (OR 1.82, 95% CI 1.03 to 3.23 and 1.96, 95% CI 1.15 to 3.34); 'warning' APH (OR 3.39, 95% CI 1.07 to 10.74 and OR 4.10, 95% CI 1.65 to 10.20).

Pre-pregnancy factors associated with PPH ≥1500 ml but not with lesser estimated blood loss were: major placenta praevia (OR 3.67, 95% CI 1.26 to 10.71) minor placenta praevia (OR 6.66, 95% CI 1.25 to 35.89) all women with anterior placenta praevia lost at least 1500 ml (OR 12.30, 95% CI 4.49 to 33.72); and steroids for fetal reasons (OR 2.06, 95% CI 1.25 to 3.40) (Table 7.3b).

Table 7.3b: Current pregnancy variables associated with postpartum haemorrhage (PPH) ≥1000 ml and ≥1500 ml in women who have bled ≥500 ml

Variable	Odds Ratio (OR) (95% CI)	
	≥1000 ml (women with PPH ≥500 ml)	**≥1500 ml (women with PPH ≥500 ml)**
Group B: Pregnancy		
v) Current pregnancy		
Multiple pregnancy	1.30 (0.68 to 2.48)	1.47 (0.80 to 2.70)
Number of fetuses	1.24 (0.68 to 2.24)	1.44 (0.82 to 2.53)
Antenatal admissions	0.93 (0.66 to 1.31)	0.84 (0.58 to 1.23)
Admissions>24/40	0.86 (0.61 to 1.21)	0.80 (0.54 to 1.18)
sBP at booking (for each 10mmHg)	1.02 (0.92 to 1.14)	1.02 (0.90 to 1.15)
Booking sBP ≧140 mmHg	1.41 (0.56 to 3.53)	1.05 (0.41 to 2.68)
Booking sBP ≧160 mmHg	0.20 (0.02 to 2.21)	0.54 (0.05 to 5.96)
dBP at booking (for each 10mmHg)	1.10 (0.95 to 1.27)	1.05 (0.89 to 1.24)
Booking dBP ≧90 mmHg	1.72 (0.57 to 5.14)	1.57 (0.57 to 4.38)
Booking dBP ≥100 mmHg	1.20 (0.12 to 11.62)	1.85 (0.20 to 16.71)
vi) Antenatal day Unit (ADU)		
Any ADU attendance	1.09 (0.84 to 1.42)	1.25 (0.91 to 1.72)
>1 ADU attendance	1.04 (0.90 to 1.20)	1.08 (0.92 to 1.27)
Abdominal pain	0.82 (0.59 to 1.15)	0.91 (0.63 to 1.31)
Itching	1.22 (0.57 to 2.62)	1.20 (0.55 to 2.63)
Fainting/ dizziness	1.78 (0.72 to 4.37)	1.27 (0.54 to 3.00)
IM iron	$	$
ECV	0.65 (0.27 to 1.60)	0.90 (0.59 to1.37)
Pre-eclampsia screen	1.05 (0.70 to 1.59)	0.79 (0.49 to 1.29)
CTG	0.65 (0.37 to 1.14)	0.59 (0.30 to 1.16)
Growth scan	3.68 (0.46 to29.16)	1.64 (0.35 to 7.81)
Reduced fetal movements	1.03 (0.69 to 1.53)	1.14 (0.68 to 1.88)
Possible ROM	1.06 (0.72 to 1.58)	1.23 (0.75 to 2.02)
Generally unwell (no diagnosis)	**2.33 (1.13 to 4.81)**	**2.30 (1.09 to 4.88)**
Possible UTI	2.44 (0.15 to 39.22)	$
Severe headaches	$	**$**
ADU for APH (no admission)	1.30 (0.71 to 2.40)	1.60 (0.87 to 2.92)
Chest pain/shortness of breath	0.68 (0.25 to 1.85)	1.29 (0.46 to 3.59)
vii) Placenta praevia		
Placenta praevia	**3.80 (1.21 to 11.93)**	**4.86 (1.99 to 11.87)**
Major placenta praevia	3.41 (0.86 to 13.51)	**3.67 (1.26 to 10.71)**
Minor placenta praevia	4.09 (0.52 to 32.09)	**6.66 (1.25 to 35.89)**
Anterior placenta praevia	NA	**12.30 (4.49 to 33.72)**
Posterior placenta praevia	1.41 (0.41 to 4.87)	2.41 (0.74 to 7.86)
viii) APH and UTI		
APH	**1.82 (1.03 to 3.23)**	**1.96 (1.15 to 3.34)**
"Warning" APH	**3.39 (1.07 to 10.74)**	**4.10 (1.65 to 10.20)**
UTI	1.10 (0.71 to 1.71)	1.12 (0.69 to 1.82)
>1 UTI	1.09 (0.75 to 1.60)	1.10 (0.72 to 1.68)
ix) Pre-eclampsia and anaemia		
Gestational hypertension	0.83 (0.45 to 1.55)	0.74 (0.39 to 1.41)
Pre-eclampsia (all)	0.88 (0.45 to 1.70)	0.76 (0.39 to 1.50)
Pre-eclampsia <34/40	1.47 (0.40 to 5.36)	0.73 (0.21 to 2.51)

Pre-eclampsia >34/40	0.69 (0.34 to 1.42)	0.78 (0.35 to 1.72)
Anaemia <10.5 g/ml	1.29 (0.89 to 1.86)	1.27 (0.84 to 1.92)
Anaemia <11.1 g/ml	1.11 (0.83 to 1.48)	1.05 (0.74 to 1.48)
Polyhydramnios	$	6.57 (0.41 to 10.71)
x) Medications pre-birth (in the week before birth)		
Allergy medications	0.96 (0.40 to 2.30)	1.16 (0.46 to 2.90)
Anti- eclampsia	2.85 (0.35 to 23.30)	1.97 (0.37 to 10.67)
Antibiotics	1.07 (0.78 to 1.45)	1.08 (0.76 to 1.53)
Antidepressants/mood disorders	1.63 (0.63 to 4.20)	1.22 (0.39 to 3.82)
Antiemetics	1.17 (0.71 to 1.93)	0.89 (0.50 to 1.57)
Antihypertensives (including for pre-eclampsia)	0.95 (0.62 to 1.48)	0.79 (0.50 to 1.27)
Aspirin	1.07 (0.57 to 2.02)	1.02 (0.55 to 1.91)
Asthma medication	1.08 (0.52 to 2.23)	0.47 (0.22 to 1.00)
Blood thinner	1.48 (0.74 to 2.56)	1.39 (0.75 to 2.58)
Medications for diabetes	0.88 (0.42 to 1.83)	0.91 (0.42 to 2.00)
Steroids for fetal reasons	1.45 (0.91 to 2.31)	**2.06 (1.25 to 3.40)**
Oral iron	1.37 (0.99 to 1.88)	1.40 (0.99 to 2.00)
Steroids for maternal reasons	1.26 (0.55 to2.88)	1.67 (0.69 to 4.02)
Pain relief	0.93 (0.45 to 1.92)	1.38 (0.65 to 2.91)
Threatened preterm birth	0.68 (0.25 to 1.85)	0.65 (0.21 to 2.04)
Thyroid disease	1.40 (0.55 to3.58)	2.04 (0.75 to 5.57)
URSO	$	$

Not applicable, NA; all women had estimated blood loss >1000 ml; numbers too small, $; systolic blood pressure, sBP; diastolic blood pressure, dBP; antenatal day unit, ADU; intramuscular, IM; external cephalic version, ECV; cardiotocograph, CTG; rupture of membranes, ROM; urinary tract infection, UTI; antepartum haemorrhage, APH.

7.5.3 Intrapartum factors associated with PPH ≥1000 ml and ≥1500 ml

Intrapartum factors associated with PPH progression to ≥1000 ml although not to ≥1500 ml are shown in Table 7.3c and included: total birth weight (OR 1.25, 95% CI 1.04 to 1.51); macrosomia >4 kg (OR 1.64, 95% CI 1.11 to 2.41). Active management of third stage of labour with oxytocin (Syntocinon®) IM (OR 2.40, 95% CI 1.23 to 4.69).

Intrapartum factors associated with progression to both ≥1000 ml and ≥1500 ml included: retained placenta (OR 1.92, 95% CI 1.04 to 3.54 and OR 1.76, 95% CI 1.01 to 3.06); and interval to suturing of genital tract trauma (OR 1.33, 95% CI 1.11 to 1.59 and OR 1.44, 95% CI 1.21 to1.72) (Table 7.3c).

Negatively associated factors for PPH ≥1000 ml and ≥1500 ml, shown in Table 7.3c, included: No labour onset (prelabour CS) (OR 0.68, 95% CI 0.49 to 0.94 and 0.56, 95% CI 0.38 to 0.84); no duration of ROM at CS (OR 0.38, 95% CI 0.22 to 0.63 and 0.21, 95% CI 0.12 to 0.37). Spinal anaesthesia (OR 0.51, 95% CI 0.38 to 0.68 and OR 0.37, 95% CI 0.25 to 0.54). Elective CS (OR 0.40, 95% CI 0.27 to 0.60 and 0.20, 0.13 to 0.33). Emergency CS (OR 0.71, 95% CI 0.50 to 1.00 and 0.37, 0.25 to 0.55).

Table 7.3c also shows third stage management negatively associated with PPH ≥1000 ml and ≥1500 ml were: prophylactic oxytocin (Syntocinon®) IV bolus (OR 0.69, 95% CI 0.52 to 0.90 and OR 0.44, 95% CI 0.32 to 0.60) and oxytocin (Syntocinon®) 40/50 IU infusion commenced (OR 0.62, 95% CI 0.48 to 0.81 and 0.46, 95% CI 0.34 to 0.63). Duration of ROM, 6-12 hours (OR 0.45, 95% CI 0.27 to 0.75); duration of ROM, 12-24 hours (OR 0.57, 95% CI 0.34 to 0.96); epidural analgesia (OR 0.71, 95% CI 0.52 to 0.97), instrumental vaginal birth (OR 0.45, 95% CI 0.29 to 0.70); and unknown interval to suturing genital tract trauma (OR 0.56, 95% CI 0.32 to 0.95) were all negatively associated with PPH ≥1500 ml.

Table 7.3c: Intrapartum variables associated with postpartum haemorrhage (PPH) to ≥1000 ml and ≥1500 ml.

Variable	Odds Ratio (OR) (95% CI)	
	≥1000 ml (women with PPH ≥500 ml)	**≥1500 ml (women with PPH ≥ 500 ml)**
Group C: Labour and birth		
xi) gestation at birth		
Gestational age at birth	1.01 (0.95 to 1.07)	0.96 (0.91 to 1.02)
xii) Birth weight		
Maximum birth weight (kg)	1.25 (1.04 to 1.51)	1.16 (0.93 to 1.44)
Total birth weight (kg)	**1.25 (1.04 to 1.51)**	1.06 (0.83 to 1.35)
Macrosomia >4 kg	**1.64 (1.11 to 2.41)**	1.21 (0.76 to 1.95)
Macrosomia >4.5kg	1.21 (0.60 to 2.43)	0.81 (0.38 to 1.71)
xiii) Onset of labour		
Spontaneous onset (reference group)		
Augmented	0.98 (0.55 to 1.76)	1.21 (057 to 2.58)
Induced	1.10 (0.77 to 1.57)	0.89 (0.60 to 1.33)
None (prelabour CS)	**0.68 (0.49 to 0.94)**	**0.56 (0.38 to 0.84)**
Duration of ROM (days)	0.97 (0.79 to 1.20)	0.93 (0.70 to 1.23)
Duration of ROM (hours)		
< 1h reference group		
1-2 h	1.00 (0.42 to 2.41)	1.55 (0.61 to 3.97)
2-3 h	0.89 (0.39 to 2.05)	0.83 (0.30 to 2.31)
3-6 h	0.80 (0.44 to 1.46)	0.68 (0.35 to 1.29)
6-12 h	0.72 (0.43 to 1.22)	**0.45 (0.27 to 0.75)**
12-24 h	0.73 (0.44 to 1.22)	**0.57 (0.34 to 0.96)**
24+ h	0.81 (0.46 to 1.43)	0.80 (0.43 to 1.50)
Length of ROM unknown	0.62 (0.38 to 1.01)	**0.42 (0.25 to 0.68)**
No ROM/ROM at CS	**0.38 (0.22 to 0.63)**	**0.21 (0.12 to 0.37)**
Dinoprostone	1.01 (0.72 to 1.43)	0.98 (0.66 to 1.45)
Dinoprostone None reference group		
Dinoprostone x 1	0.92 (0.61 to 1.39)	0.85 (0.53 to 1.38)
Dinoprostone x 2+	1.20 (0.70 to 2.06)	1.23 (0.67 to 2.24)
xiv) Intrapartum		
Oxytocin (Syntocinon®)	1.13 (0.86 to 1.49)	0.81 (0.58 to 1.14)
Duration of oxytocin (Syntocinon®) (hours)	1.02 (0.97 to 1.06)	1.03 (0.98 to 1.08)
Spinal anaesthesia	**0.51 (0.38 to 0.68)**	**0.37 (0.25 to 0.54)**
Epidural analgesia	0.95 (0.73 to 1.24)	**0.71 (0.52 to 0.97)**
Temperature		
37.2°C	1.17 (0.83 to 1.64)	0.92 (0.62 to 1.38)
37.5°C	1.23 (0.75 to 2.01)	1.12 (0.64 to 1.95)
37.8°C	1.61 (0.82 to 3.15)	1.31 (0.62 to 2.78)
38.0°C	2.14 (0.82 to 5.62)	2.49 (0.92 to 6.69)
Temperature unrecorded	0.83 (0.63 to 1.10)	0.73 (0.53 to 1.01)
Evidence of Chorioamnionitis	3.50 (0.57 to 21.57)	**4.65 (1.09 to 19.89)**
xv) Birth		
Mode of birth – SVD (Reference group		
Instrumental vaginal birth	0.70 (0.47 to 1.06)	**0.45 (0.29 to 0.70)**
Elective CS	**0.40 (0.27 to 0.60)**	**0.20 (0.13 to 0.33)**
Emergency CS	**0.71 (0.50 to 1.00)**	**0.37 (0.25 to 0.55)**

xvi) Third stage of labour		
Physiological third stage	1.29 (0.71 to 2.36)	**3.18 (1.75 to 5.77)**
Oxytocin (Syntocinon ®) IM	**2.40 (1.23 to 4.69)**	1.83 (0.83 to 4.02)
Oxytocin (Syntocinon®) IV (bolus)	**0.69 (0.52 to 0.90)**	**0.44 (0.32 to 0.60)**
Ergometrine Maleate/Oxytocin (Syntometrine®) IM	1.22 (0.91 to 1.63)	**1.63 (1.15 to 2.29)**
Oxytocin (Syntocinon®) IV (increased)	1.03 (0.64 to 1.68)	0.71 (0.42 to 1.18)
Oxytocin (Syntocinon®) 40/50 IU (infusion commenced)	**0.62 (0.48 to 0.81)**	**0.46 (0.34 to 0.63)**
Retained placenta	**1.92 (1.04 to 3.54)**	**1.76 (1.01 to 3.06)**
Interval to suturing (genital tract trauma)	**1.33 (1.11 to 1.59)**	**1.44 (1.21 to 1.72)**
Interval to suturing not known	0.78 (0.49 to 1.25)	**0.56 (0.32 to 0.95)**

Caesarean section, CS; rupture of membranes, ROM; spontaneous vaginal delivery, SVD; intramuscular, IM; intravenous, IV.

7.6 Other indicators of severe blood loss

7.6.1 Blood transfusion

Overall 3.9% (95%CI 3.2 to 4.6) received a blood transfusion, the contribution of each Centre is shown in Table 7.4, the increased use in Centre 1 may represented the added complexity of the tertiary referral Centre. Despite both Centres having cell salvage available, only 1 woman, in Centre 2, received autologous transfusion. Twelve women received O rhesus negative blood, and 1 received ABO matched blood. Other blood products were utilised sparingly with minimal use of cryoprecipitate in both Centres and no fibrinogen used in Centre 2.

Table 7.4: Blood transfusion rates in each Centre and combined

Centre	Number of women/women represented	% received blood transfusion	95% Confidence Interval
Centre 1	308/6731	4.6%	3.5 to 5.6
Centre 2	79/3206	2.4%	1.7 to 3.2
All	384/9937	3.9%	3.2 to 4.6

7.6.2. Repair trauma and use of haemostatic suturing techniques

Completion of genital tract trauma was effective at ameliorating blood loss prior to 1000 ml in 158 cases (132 in Centre 1 and 24 in Centre 2).

In this cohort 9% of PPH ≥500 ml were treated by insertion of haemostatic suturing. Insertion of haemostatic sutures ameliorated blood loss before reaching 1000 ml at CS in 199 women and following vaginal delivery for 24 women.
Overall 155 women lost ≥1000 ml, required haemostatic sutures to arrest blood loss (134 following caesarean and 21 following vaginal birth, see Table 7.4).

7.6. 3 Manual removal of placenta/ placental delivery

Placental delivery, was undertaken in 3.5% of this cohort as an action to arrest bleeding (3.16%, 77/2430 in Centre 1; 4.0%, 26/649 in Centre 2). In these data most placentas were delivered within 2 hours. The longest delay in Centre 1 was 4 hour 56 min, documented estimated blood loss 1300 ml, and in Centre 2 was 4

hour 5 min, documented estimated blood loss 1500 ml. Both cases were managed conservatively, as initial blood loss settled, but there was a subsequent substantial loss per vaginum, and manual removal was undertaken expediently.

7.6.4 Vaginal packing and balloon tamponade

Vaginal packing was employed in 24 women (1.2%) with EBL 500-999 ml in Centre 1 and none in Centre 2. In PPH ≥1000 ml, 6.9% of women were treated with a vaginal pack, 37 women in Centre 1 and 17 in Centre 2.

Balloon tamponade was rarely employed in this cohort, and reserved for those who lost at least 1000 ml. In total 21 women received this treatment, 2.7% of those with PPH ≥1000 ml.

7.6.5 Interventional radiology

Despite the availability of interventional radiology on both sites, and cited as an effective treatment in both protocols, ligation of the uterine or internal iliac arteries was undertaken in 1 case (Centre 1). This concurs with the findings of others regarding limited experience of these procedures (Webster *et al*., 2010).

7.6.6 Hysterectomy

There were 5 peripartum hysterectomies among 9935 births, a rate of 0.50 per 1000 births, summary data regarding these are shown in Table 7.5.

The majority (4/5) were undertaken in Centre 1, which may reflect the complex cases referred to this tertiary Centre. Eighty percent of these procedures were

undertaken in women with previous CS, confirming both the established association with uterine rupture and abnormal placentation reported previously (Al-Zirqi *et al.,* 2010; Chattopadhyay *et al*., 1993). Eighty percent were also of Black African ethnicity, immigration history was not collected and therefore it is not possible to assess whether these women were born outside the UK, a factor noted as relevant in the most recent Confidential Enquiry into maternal death two women requiring peripartum hysterectomies registered late for antenatal care, another factor identified in the same report (CMACE, 2011). All but one of the women were over-weight or obese, and given the increasing numbers of women entering pregnancy with high BMIs, this underlines the importance of identifying effective strategies to improve pregnancy outcomes for heavier women (Oteng-Ntim *et al*., 2012).

Table 7.5: Summary data for women requiring peripartum hysterectomy to control bleeding.

ID and Centre	Previous history	Details	Blood Loss
Centre 1: 266	White British 35 years BMI 23.1 G2 P1 Emergency CS for breech- not detected prior to full dilatation	Admitted in spontaneous labour, screaming in pain. Sudden bradycardia. Emergency CS for uterine rupture. Transferred to HDU, continued bleeding, uterine atony. Transferred back to theatre EUA proceeded to hysterectomy.	EBL at CS 1200 ml No further blood loss entered on electronic records. Addition of subsequent measured BL 7037 ml TOTAL Blood Loss 8237 ml
Centre 1: 669	African 27 years BMI 37.9 G4 P3 Previous CS x3	Late booker Placenta percreta suspected antenatally - radiology booked for elective CS, cross matched 6 units. Hb 9.1 prior to delivery. CS in interventional radiology theatre. Interventional radiology inserted balloons to both uterine vessels prior to delivery of baby. Placenta	Consultant estimated BL 8000 ml. Anaesthetist and others present estimated 15000 ml.

		partially separated - bleeding heavily. Cell salvage connected. Interventional radiology used embolization. Proceeded to total abdominal hysterectomy, performed by consultant gynaecologist. Urologist present for hysterectomy.	
Centre 1: 1367	South American 37 years BMI 30.8 G4 P3 Previous CSx1	"Type IV placenta praevia, in labour - placenta encountered and baby delivered as breech through placenta in good condition. Placenta partially adherent and profuse bleeding seen originating from lower uterine segment. Anterior wall of uterus very thin probably due to placenta accreta. Rapid loss of blood - decision to perform hysterectomy taken." To ITU, but as no bed on HDU.	Doctor estimated blood loss as 6000 ml Midwife measured blood loss as 6615 ml
Centre 1: 1022	Black African 32 years BMI 26.9 G3 P1 Previous CSx1	Late booker - unaware of pregnancy. Massive PPH at CS- atonic uterus, and bleeding from placental bed. Received 4 units RBC and 4 units FFP in theatre - medical attempts not effective, therefore hysterectomy performed. Further 2 units blood transfused postnatally.	Estimated blood loss by anaesthetist 3000-3500 ml Estimated blood loss by ST3 and Registrar present 4000 ml Documented variably in notes as 3 l, and 4 l - no definitive blood loss volume.
Centre 2: 2049	Black African 32 years BMI 29.8 G3 P2 No previous CS No previous PPH	Arrived in labour ward in second stage. Proceeded rapidly to SVD. 2nd degree tear. Atonic uterus.	8500 ml

7.6.7 Transfer to HDU/ITU

Overall 86 (2.6%) women were transferred for high dependency or intensive care following PPH; 66 in Centre 1 and 20 in Centre 2.

Due to variation in practice, with some units providing complex care, including mechanical ventilation in obstetric dependency units, whilst those without such facilities transfer women to general intensive care units, comparison with other data is problematic. The Scottish Audit provides details of ITU admission where availability exists, but admissions are recorded as none in the absence of high dependency areas (Lennox, 2007). Reviews of admissions in Europe and Australia have also reported difficulties but suggest 0.7% of ITU admissions are associated with maternal morbidity and major obstetric haemorrhage is the most common complication necessitating admissions (Crozier and Wallace, 2011; Keizer *et al*., 2006).

7.7 Summary

The aim of the analyses in this chapter was to ascertain the impact of pre-pregnancy, pregnancy acquired and intrapartum variables on mean estimated blood loss and PPH and different thresholds.

Factors associated with PPH at different levels (≥500 ml; ≥1000 ml; ≥1500 ml) were inconsistent, with many being both causative and preventative at thresholds. Many previously identified factors that increase or attenuate risk of PPH have been confirmed, including: maternal age; BMI; ethnicity; primiparity; multiparity; maternal smoking; previous PPH; previous CS; placenta praevia; obstetric

cholestasis; induction and augmentation of labour; instrumental vaginal delivery; CS (elective and emergency); evidence of chorioamnionitis; interval to suturing. Additionally the complexity of different factors impact on estimated blood loss following birth has been highlighted. Further statistical modeling is required to investigate the relative and cumulative impact of factors and the effect of interventions and actions that may attenuate blood loss. This is undertaken and reported in Chapter 8.

Chapter 8: Results 3; construction of statistical models to improve the prediction of postpartum haemorrhage ≥500 ml, ≥1000 ml and ≥1500 ml

Introduction

Due to the inconsistent influence of the individual factors shown in previous analyses further investigation was required in order to assess the relative contribution of each factor, identification of those factors with greatest impact, and the cumulative effects of multiple factors that may increase and attenuate risk of PPH. Multiple regression modeling was employed to investigate the impact of sequentially introduced variables.

Factors were selected from those employed in previous analyses (Chapters 6 and 7) on the basis of statistical significance, 95% p values, rather than Odds Ratios (OR) and confidence intervals (CI). The rationale for this being, that although a high OR indicates a high risk with a particular exposure, when that exposure is rare, it is unlikely to be significant, with wide confidence intervals, and therefore the impact on the overall event rate is low (Coggan, 2003; Field, 2009).

Overall the number of factors needed to be reduced in order to a) ensure the behaviour of the model for the model fitting process, and b) maximise the practical usefulness of the model. The aim of the modeling was to identify a small number of statistically and clinically significant factors. Excessive numbers of factors would lead to reduced performance of the model in terms of it poorly discriminating those at risk. Factor selection was decided by clinical significance, defined as OR >2 (Coggan, 2003) or p=0.05 (Field, 2009). It has been proposed that when OR ≥2 but the confidence intervals cross one, caution should be exercised when claiming no clinical significance, as this can often be attributed to low numbers or outliers (Coggan, 2003).

8.1 Risk factor modeling according to chronological sequence

Multiple regression analysis was undertaken adding factors in chronological order to identify sequential risk factors for PPH acquired within the three groups A) pre-pregnancy, B) during pregnancy, and C) labour and birth, and the 15 subgroups. This technique is similar to that described in hierarchical regression (blockwise entry), however the factors selected were from our own dataset and not those previously identified by others, as traditionally used in this technique (Field, 2009). After the preliminary inclusion of all factors, those without clinical significance (OR<2 or confidence intervals crossing 1) (Coggan, 2003) or statistical significance (p=>0.05) were eliminated from the model (Field, 2009).

This precluded the use of control variables, (irrespective of statistical significance) employed in some modeling techniques, concomitantly each factor was treated as

a predictor, with none considered as a control factor and consequently no adjusted results were produced (Field, 2009).

8.2 Risk pathways for PPH ≥500 ml

Table 8.1 shows the full regression model of the risk pathway for PPH ≥500 ml, resulting from 3 regression models selecting principal factors in groups A) pre-pregnancy, B) pregnancy health and events and C) intrapartum, birth and third stage management, and removing all those that fail to reach clinical or statistical significance.

Group A) Pre-pregnancy risk factors reaching clinical or statistical significance included: maternal age (OR 1.45, 95% CI 1.19 to 1.76, p= <0.000); Black African ethnicity (OR 1.77, 95% CI 1.31 to 2.39, p= 0.000); BMI (OR 1.03, 95% CI 1.01 to 1.05, p=0.006); assisted conception (OR 2.93, 95% CI 1.30 to 6.59, p=0.010) and previous PPH (OR 2.34, 95% CI 1.30 to 6.59 p=0.003) with only multiparity with no previous CS attenuating risk (OR 0.33, 95% CI 0.26 to 0.42, p=0.000).

With the addition of the factors in group B, pregnancy health and events, maternal age (OR 1.44, 95% CI 1.18 to 1.75, p=<0.000) remained, as did Black African ethnicity (OR 1.77, 95% CI 1.30 to 2.41, p=0.000) and BMI (OR 1.03, 95% CI 1.00 to 1.05 p=0.016). Assisted conception remained in the model although now marginally insignificant (OR 2.28, 95%CI 0.99 to 5.29 p=0.054) and previous PPH (OR 2.45, 95% CI 1.38 to 4.35, p=0.002). Multiparity with no previous CS remained protective (OR 0.33, 95% CI 0.25 to 0.42, p=0.000). Added to these were multiple pregnancy (OR 2.27, 95% CI 1.04 to 4.96,

p=0.039), 'warning' APH (OR 8.95, 95% CI 1.02 to 78.7, p=0.048) and pre-eclampsia (OR 3.16, 95% CI 1.12 to 8.93, p=0.030).

All women with placenta praevia, regardless of degree and position, lost ≥500 ml, and therefore this variable was omitted from the prediction model for PPH ≥500 ml as it provided 100% prediction (risk ratio 100%). If included, the effect of this factor was so strong, the influence of other factors would not be apparent. We originally ran the model including placenta praevia, and it did, indeed, supersede all other factors.

With the introduction of group C) Intrapartum, birth and third stage management variables age, assisted conception techniques, multiparity with no previous CS, multiple pregnancy and 'warning' APH failed to reach statistical significance. Only Black African ethnicity (OR 1.94, 95% CI 1.35 to 2.79, p=0.000) and previous PPH (OR 2.75, 95% CI 1.40 o 5.44, p=0.003) maintained statistical significance. Newly added significant factors were maximum birth weight (OR 2.19, 95% CI 1.62 to 2.99, p=0.000); raised temperature in labour, per degree >37°C (OR 2.62, 95% CI 1.24 to 5.52, p=0.001); instrumental vaginal delivery (OR 3.50, 95% CI 2.21 to 5.24, p=0.000); elective CS (OR 24.4, 95% CI 5.53 to 108.0, p=0.000); emergency CS (OR 40.5, 95% CI 16.30 to 101.0, p=0.000); retained placenta (OR 21.3, 95% CI 8.31 to 54.70, p=0.000) interval to suturing (2.03, 95% CI 1.65 to 2.50, p=0.000) and interval to suturing not known (OR 2.20, 95% CI 1.32 to 3.69, p=0.003) .

Conversely, Ergometrine Maleate/Oxytocin (Syntometrine®) IM (OR 0.55, 95% CI 0.33 to 0.91, p=0.019) and oxytocin (Syntocinon®) 40/50 IU infusion (OR

0.61, 95% CI 0.38 to 0.99, p=0.045) were protective for PPH ≥500ml. This information is shown diagrammatically in Figure 8.1. Whilst the majority of factors either clinically or statistically increasing risk of PPH ≥500ml occurred as a result of intrapartum or birth events, the only factor remaining significant from earlier inclusion were Black African ethnicity and previous PPH. There were several factors that, although initially statistically significant at inclusion, the subsequent addition of hierarchical factors rendered insignificant in the final model. These included: assisted conception techniques, maternal age and multiple pregnancy.

Similarly multiparity with no previous CS was protective initially but was not statistically significant in the final model.

Within the 16 subgroups several had no significant associations with PPH ≥500 ml, these were: Sub-group 2) local deprivation; 5) current pregnancy; 6) day unit attendances; 8) APH and UTI; 11) gestation at birth; 13) onset of labour.

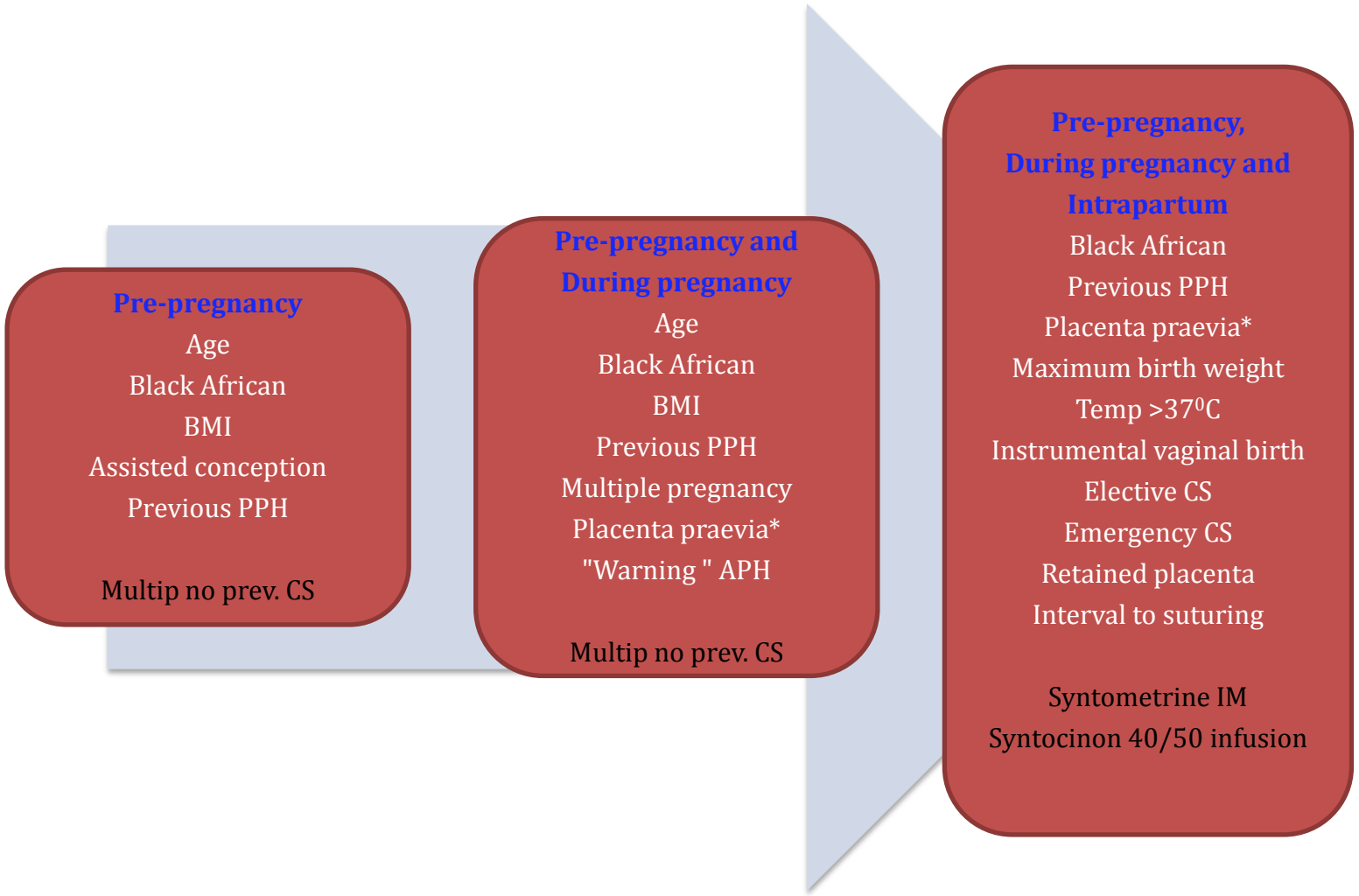
Table 8.1: Risk pathways for postpartum haemorrhage (PPH) ≥500 ml according to chronological variables grouped as pre-pregnancy, pregnancy, labour and birth. Full regression model; result of three multiple regression models selecting the principal significant variables. In each model, an additional group of predictors is added. Results adjusted for other members of the same group and for previous groups only.

Risk factors included in final model	**Pre-Pregnancy** Variable subgroups 1-4 (1895 women included) **OR (95% CI), p**	**During Pregnancy** Variable subgroups 1-10 (1868 women included; 27 excluded due to 1 missing data and 26 perfectly predicted) **OR (95% CI), p**	**Labour and Birth** Variable subgroups 1- 16 (1724 women included; 171 excluded due to 135 missing data, 36 perfectly predicted) **OR (95% CI), p**
1) **Sociodemographic**			
Age, for each 10 years	**1.45 (1.19 to 1.76), 0.000**	**1.44 (1.18 to 1.75), 0.000**	0.93 (0.73 to 1.19), 0.57
Black African	**1.77 (1.31 to 2.39), 0.000**	**1.77 (1.30 to 2.41), 0.000**	**1.94 (1.35 to 2.79), 0.000**
2) **Local Deprivation: index of multiple deprivation, most deprived UK quintile (%)**			
Barriers to housing and services	1.06 (0.87 to 1.33), 0.61	1.05 (0.83 to 1.32), 0.69	1.04 (0.79 to 1.36), 0.80
Education, skills and training	0.93 (0.64 to 1.36), 0.72	0.93 (0.64 to 1.36), 0.71	1.03 (0.57 to 1.62), 0.89
3) **General and medical risk factors**			
Current smoker	0.76 (0.54 to 1.09), 0.14	0.77 (0.53 to 1.10), 0.15	0.82 (0.53 to 1.28), 0.38
BMI (kg/m^2)	**1.03 (1.01 to 1.05), 0.006**	**1.03 (1.00 to 1.05), 0.016**	1.01 (0.99 to 1.04), 0.32
Assisted conception	**2.93 (1.30 to 6.59), 0.010**	2.28 (0.99 to 5.29), 0.054	2.10 (0.83 to 5.33), 0.19
4) **Previous obstetric history**			
Previous PPH	**2.34 (1.33 to 4.12), 0.003**	**2.45 (1.38 to 4.35), 0.002**	**2.75 (1.40 to 5.44), 0.003**
Multiparous previous Caesarean	1.32 (0.93 to 1.87), 0.19	1.30 (0.91 to 1.86), 0.14	0.96 (0.61 to 1.51), 0.86
Multiparous no previous Caesarean	**0.33 (0.26 to 0.42), 0.000**	**0.33 (0.25 to 0.42), 0.000**	0.79 (0.56 to 1.11), 0.18
5) **Current pregnancy**			
Multiple pregnancy		**2.27 (1.04 to 4.96), 0.039**	2.02 (0.82 to 5.00), 0.13
Admissions >24 weeks		0.82 (0.57 to 1.18), 0.28	0.82 (0.53 to 1.29), 0.39
6) **Antenatal day unit (ADU) attendances**			
Any ADU attendance		1.06 (0.84 to 1.34), 0.62	0.95 (0.72 to 1.26), 0.74
Preeclampsia screen		1.06 (0.65 to 1.75), 0.81	1.04 (0.57 to 1.91), 0.89
Generally unwell		1.22 (0.68 to 2.18), 0.50	1.33 (0.69 to 2.60), 0.40
7) **Placenta praevia**: All 26 women with major or anterior placenta praevia PPH ≥500 ml			
8) **Antepartum haemorrhage (APH) & urinary tract infection**			
APH		1.11 (0.62 to 1.99), 0.74	1.27 (0.65 to 2.51), 0.48
'Warning APH'		**8.95 (1.02 to 78.7), 0.048**	1.92 (0.19 to 19.3), 0.58
9) **Pre-eclampsia (PET) and anaemia**			
Gestational hypertension		1.83 (0.83 to 4.03), 0.13	2.22 (0.87 to 5.63), 0.093

Pre-eclampsia		**3.16 (1.12 to 8.93), 0.030**	3.21 (0.94 to 10.90), 0.062
10) **Medications in pregnancy pre-birth**			
Antibiotics		1.35 (1.01 to 1.80), 0.043	1.14 (0.77 to 1.66), 0.52
Antihypertensives (including for PET)		0.75 (0.44 to 1.29), 0.30	0.66 (0.33 to 1.32), 0.24
Diabetic Rx		1.89 (0.79 to 4.56), 0.15	1.20 (0.43 to 3.37), 0.73
Steroids for fetal reasons		0.90 (0.57 to 1.43), 0.65	1.23 (0.69 to 2.18), 0.49
11) **Gestation at birth**			
Gestation at delivery (weeks)			0.98 (0.90 to 1.08), 0.70
12) **Birth weight**			
Maximum birth weight (Kg)			**2.19 (1.62 to 2.99), 0.000**
13) **Onset of labour**			
No labour onset			1.51 (0.47 to 4.90), 0.49
Induction			0.75 (0.39 to 1.46), 0.40
Augmentation			0.83 (0.42 to 1.64), 0.59
ROM >2 hours before onset			0.95 (0.64 to 1.41), 0.79
ROM >6 hours before onset			1.35 (0.90 to 2.02), 0.14
ROM not recorded			1.03 (0.60 to 1.77), 0.91
14) **Intrapartum**: all 10 women with evidence of chorioamnionitis PPH ≥ 500 ml			
Dinoprostone			1.04 (0.53 to 2.02), 0.91
Oxytocin (Syntocinon®)			1.44 (0.95 to 2.16), 0.085
Spinal anaesthesia			0.87 (0.51 to 1.49), 0.60
Epidural analgesia			1.08 (0.71 to 1.65), 0.71
Raised temperature (per degree>37.0°C)			**2.62 (1.24 to 5.52), 0.011**
Temperature not recorded			0.75 (0.50 to 1.11), 0.15
15) **Birth**			
Instrumental vaginal			**3.50 (2.21 to 5.24), 0.000**
Elective Caesarean			**24.4 (5.53 to 108.00), 0.000**
Emergency Caesarean section			**40.5 (16.30 to 101.00), 0.000**
16) **Third stage**			
Physiological			1.48 (0.80 to 2.77), 0.22
Ergometrine Maleate/Oxytocin (Syntometrine®) IM			**0.55 (0.33 to 0.91), 0.019**
Oxytocin (Syntocinon®) IV bolus			0.58 (0.27 to 1.25), 0.17
Oxytocin (Syntocinon®) 40/50 IU infusion started			**0.61 (0.38 to 0.99), 0.045**
Retained placenta			**21.3 (8.31 to 54.70), 0.000**

Suture interval after vaginal birth (h)			**2.03 (1.65 to 2.50), 0.000**
Suture interval not recorded			**2.2 (1.32 to 3.69), 0.003**

Figure 8.1: Diagram of multiple logistic regression and chronological regression analysis showing predictors of PPH ≥500 ml (risk factors in white, protective factors in black). Postpartum haemorrhage, PPH; body mass index, BMI; Caesarean section, CS; intramuscular, IM; antepartum haemorrhage, APH; perfect prediction *



8.3 Risk pathways for PPH ≥1000 ml

The same process was undertaken to investigate the risk pathway for PPH ≥1000 ml. Table 8.2 shows the full regression model, resulting from 3 regression models selecting principal variables in groups A) pre-pregnancy, B) pregnancy health and events and C) intrapartum, birth and third stage management, and removing all those that fail to reach clinical or statistical significance.

Group A) Pre-pregnancy risk factors reaching clinical or statistical significance include: BMI (OR 1.05, 95% CI 1.03 to 1.07, p=0.000); Black African ethnicity (1.44, 95% CI 1.12 to 1.85, p=0.005); previous PPH (OR 1.83, 95% CI 1.16 to 2.90, p=0.010). Attenuating factors were multiparity with no previous CS (OR 0.64, 95% CI 0.50 to 0.81, p=0.000) and current smoker at first antenatal appointment (OR 0.59, 95% CI 0.42 to 0.85, p=0.004).

With the addition of pregnancy health and events factors, Group B, the factors remaining significant included Black African ethnicity (OR 1.44, 95% CI 1.12 to 1.88, p=0.005); BMI (1.05, 95% CI 1.03 to 1.07, p=0.000) and previous PPH (OR 1.89, 95% CI 1.18 to 3.02, p=0.008). Multiparity with no previous CS remained protective (OR 0.62, 95% CI 0.49 to 0.80, p=0.000), as did smoking at first antenatal visit (OR 0.59, 95% CI 0.41 to 0.85, p=0.005). Added to these were multiple pregnancy (OR 2.09, 95% CI 1.17 to 3.74, p=0.013), antenatal attendance feeling 'generally unwell' (OR 1.71, 95% CI 1.03 to 2.84, p=0.039) and 'warning' APH (OR 4.23, 95% CI 1.03 to 17.4, p=0.045).

All women with anterior placenta praevia bled ≥1000 ml, and therefore this factor was omitted from the prediction model for PPH ≥1000 ml as it provided 100% prediction (risk ratio 100%). As with all degrees of placenta praevia for lesser bleeds, if included, the effect of this factor was so strong, relatively the influence of other factors would not be apparent; and as with the smaller bleeds we originally ran the model including anterior placenta praevia, and it did, indeed, supersede all other variables.

With the introduction of intrapartum, birth and third stage management variables, Group C, no earlier acquired significant risk factors became insignificant and IMD education, skills and training was added (OR 1.51, 95% CI 1.02 to 2.23, p=0.038). Newly added intrapartum significant factors were maximum birth weight (OR 1.71, 95% CI 1.35 to 2.18, p=0.000); maternal temperature in labour per degree >37°C (OR 1.74, 95% CI 1.10 to 2.75, p=0.019); oxytocin (Syntocinon®) during first or second stage of labour (induction or augmentation) (OR 1.42, 95% CI 1.02 to 1.96, p=0.037) instrumental vaginal delivery (OR 2.53, 95% CI 1.72 to 3.73, p=0.000); elective CS (OR 3.51, 95% CI 1.24 to 9.97, p=0.018); emergency CS (OR 7.05, 95% CI 3.5 to 14.2, p= 0.000); retained placenta (OR 7.51, 95% CI 4.08 to 13.8, p=0.000) interval to suturing (OR 1.74, 95% CI p=0.000) and interval to suturing not known (OR 1.74, 95% CI 1.46 to 2.08, p=0.000). Conversely, prophylactic intramuscular administration of uterotonic Ergometrine Maleate/Oxytocin (Syntometrine®) (OR 0.58, 95% CI 0.38 to 0.89, p=0.013) was protective for PPH ≥1000 ml. These results are diagrammatically represented in Figure 8.2.

In this analysis risk factors in the initial model remained statistically significant for PPH ≥1000 ml, these were Black African ethnicity, BMI and previous PPH. Current

smoking at booking also remained protective against PPH ≥1000 ml, although the protection for multiparous women with no previous CS was no longer significant once intrapartum factors were added.

Table 8.2: Risk pathways for postpartum haemorrhage (PPH) ≥1000 ml including all women and according to chronological variables grouped as pre-pregnancy, during pregnancy, labour and birth. Full regression model: result of three multiple regression models selecting the principal significant variables. In each model, a new additional group of predictors is used. Results are adjusted for other members of the same group and for previous groups only. All women included.

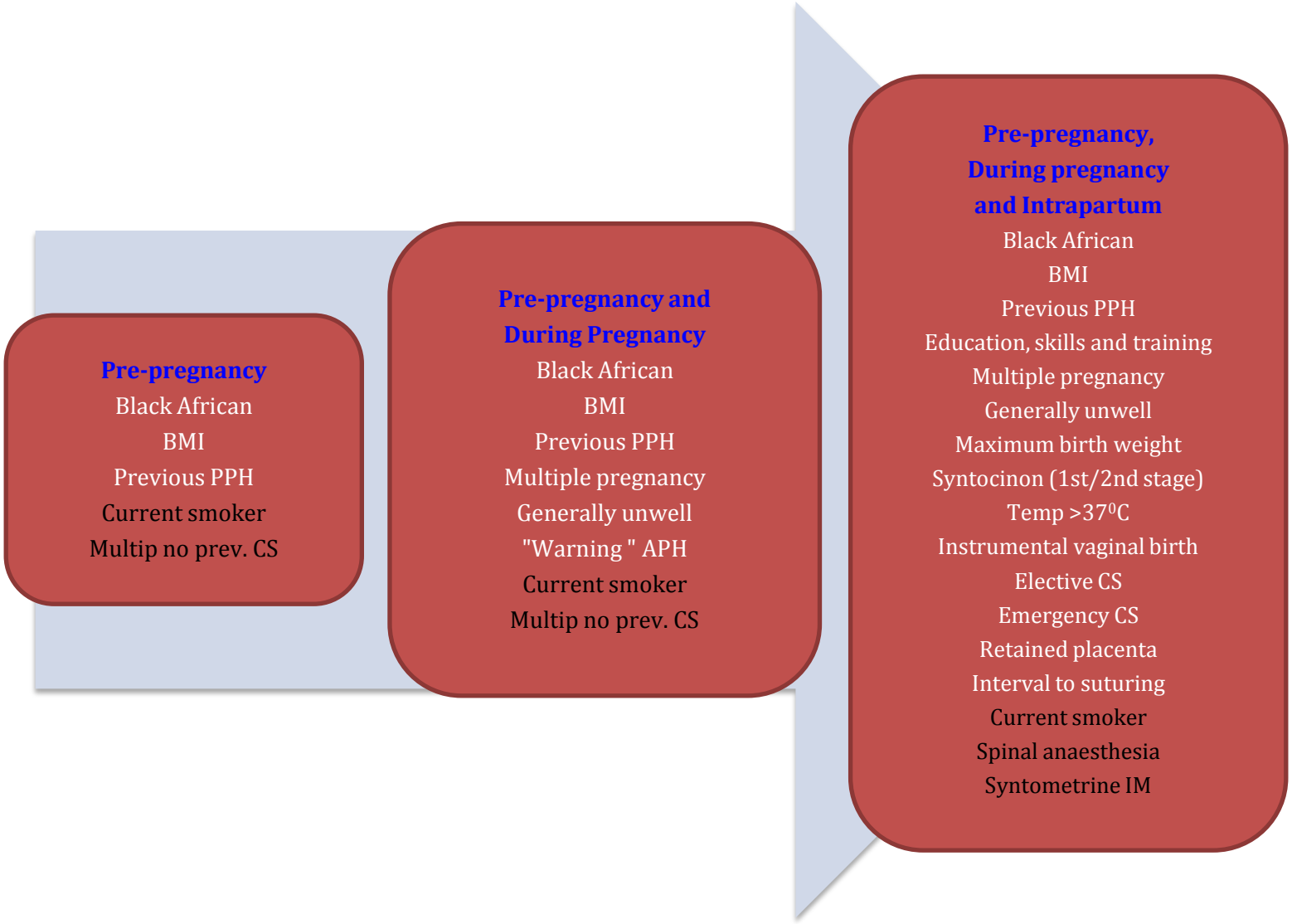
Risk factors included in final model (1785 included; 110 excluded due to missing data, 15 excluded with anterior placenta praevia as all women bled ≥1000 ml)	**Pre-Pregnancy** Variable subgroups 1-4 **OR (95% CI), p**	**During Pregnancy** Variable subgroups 1-10 **OR (95% CI), p**	**Labour and Birth** Variable subgroups 1- 16 **OR (95% CI), p**
1) **Sociodemographic**			
Age, for each 10 years	1.18 (0.99 to 1.40), 0.072	1.19 (0.99 to 1.42), 0.061	0.97 (0.79 to 1.18), 0.74
Black African	**1.44 (1.12 to 1.85), 0.005**	**1.45 (1.12 to 1.88), 0.005**	**1.50 (1.13 to 1.98), 0.005**
2) **Local Deprivation: Index of multiple deprivation, most deprived UK quintile (%)**			
Barriers to housing and services	1.07 (0.87 to 1.31), 0.54	1.05 (0.85 to 1.29), 0.66	1.01 (0.80 to 1.27), 0.94
Education, skills and training	1.32 (0.93 to 1.88), 0.12	1.34 (0.94 to 1.93), 0.11	**1.51 (1.02 to 2.23), 0.038**
3) **General and medical risk factors**			
Current smoker	**0.59 (0.42 to 0.85), 0.004**	**0.59 (0.41 to 0.85), 0.005**	**0.63 (0.42 to 0.93), 0.021**
BMI (Kg/m^2)	**1.05 (1.03 to 1.07), 0.000**	**1.05 (1.03 to 1.07), 0.000**	**1.04 (1.02 to 1.06), 0.001**
Assisted conception	1.57 (0.93 to 2.65), 0.09	1.18 (0.67 to 2.07), 0.57	1.22 (0.67 to 2.23), 0.52
4) **Previous Obstetric history**			
Previous PPH	**1.83 (1.16 to 2.90), 0.010**	**1.89 (1.18 to 3.02), 0.008**	**1.88 (1.13 to 3.11), 0.015**
Multiparous previous Caesarean	0.91 (0.69 to 1.21), 0.52	0.88 (0.66 to 1.18), 0.40	0.96 (0.68 to 1.35), 0.80
Multiparous no previous Caesarean	**0.64 (0.50 to 0.81), 0.000**	**0.62 (0.49 to 0.80), 0.000**	1.14 (0.84 to 1.55), 0.40
5) **Current Pregnancy**			
Multiple pregnancy		**2.09 (1.17 to 3.74), 0.013**	**2.33 (1.23 to 4.41), 0.009**
Admissions >24 weeks		0.77 (0.55 to 11.06), 0.11	0.86 (0.60 to 1.22), 0.40
6) **Antenatal Day Unit (ADU) attendances**			
Any ADU attendance		1.13 (0.91 to 1.4), 0.28	1.04 (0.82 to 1.32), 0.73
PET screen		1.19 (0.78 to 1.81), 0.43	1.23 (0.77 to 1.96), 0.39
Generally unwell		**1.71 (1.03 to 2.84), 0.039**	**2.03 (1.18 to 3.49), 0.011**
7) **Placenta praevia**			
Anterior		$	$
Major		0.43 (0.61 to 3.08), 0.40	0.54 (0.75 to 3.94), 0.55
8) **Antepartum haemorrhage (APH) & urinary tract infection (UTI)**			
APH		1.44 (0.86 to 2.40), 0.16	1.66 (0.96 to 2.89), 0.071
'Warning APH'		**4.23 (1.03 to 17.4), 0.045**	2.31 (0.54 to 9.96), 0.26

9) **Pre-eclampsia (PET) and anaemia**			
Gestational hypertension		0.88 (0.46 to 1.66), 0.69	0.90 (0.45 to 1.80), 0.76
Pre-eclampsia		1.13 (0.54 to 2.38), 0.74	0.90 (0.39 to 2.06), 0.80
10) **Medications in pregnancy pre-birth**			
Antibiotics		1.22 (0.95 to 1.56), 0.12	0.96 (0.71 to 1.3), 0.79
Antihypertensives (Incl. for PET)		0.99 (0.62 to 1.57), 0.95	0.95 (0.56 to 1.6), 0.84
Diabetic treatments		1.18 (0.61 to 2.3), 0.62	0.99 (0.48 to 2.03), 0.97
Steroids for fetal reasons		1.05 (0.71 to 1.58), 0.80	1.46 (0.93 to 2.3), 0.099
11) **Gestation at birth**			
Gestation at delivery (weeks)			0.99 (0.92 to 1.07), 0.87
12) **Birth weight**			
Maximum birth weight (kg)			**1.71 (1.35 to 2.18), 0.000**
13) **Onset of labour**			
No labour onset			1.58 (0.73 to 3.44), 0.25
Induction			1.11 (0.67 to 1.84), 0.69
Augmentation			1.23 (0.73 to 2.08), 0.45
ROM >2 hours before onset			1.02 (0.70 to 1.48), 0.93
ROM >6 hours before onset			1.04 (0.73 to 1.48), 0.82
ROM unknown			0.99 (0.63 to 1.56), 0.95
14) I**ntrapartum**			
Dinoprostone			0.82 (0.50 to 1.35), 0.43
Oxytocin (Syntocinon®)			**1.42 (1.02 to 1.96), 0.037**
Spinal anaesthesia			0.69 (0.47 to 1.00), 0.051
Epidural analgesia			0.97 (0.69 to 1.36), 0.85
Temperature per degree >37.0°C			**1.74 (1.10 to 2.75), 0.019**

Temperature not recorded			1.06 (0.74 to 1.51), 0.75
Chorioamnionitis			3.54 (0.66 to 19.1), 0.14
15) **Birth**			
Instrumental vaginal			**2.53 (1.72 to 3.73), 0.000**
Elective Caesarean			**3.51 (1.24 to 9.97), 0.018**
Emergency Caesarean section			**7.05 (3.5 to 14.2), 0.000**
16) **Third stage**			
Physiological			1.36 (0.77 to 2.41), 0.29
Ergometrine Maleate/Oxytocin (Syntometrine®) IM			**0.58 (0.38 to 0.89), 0.013**
Oxytocin (Syntocinon®) IV bolus			0.59 (0.31 to 1.11), 0.099
Oxytocin (Syntocinon®) 40/50 IU commenced			0.76 (0.54 to 1.06), 0.10
Retained placenta			**7.51 (4.08 to 13.8), 0.000**
Suture interval after vaginal birth (h)			**1.74 (1.46 to 2.08), 0.000**
Suture interval not recorded			1.37 (0.87 to 2.16), 0.187

Full regression model: result of three multiple regression models selecting the principal significant variables. In each model, a new additional group of predictors is used. Results are adjusted for other members of the same group and for previous groups only
Rupture of membranes, ROM; intramuscular, IM; intravenous, I

Figure 8.2: Diagram of multiple logistic regression and chronological regression analysis showing predictors of PPH ≥1000 ml (risk factors in white, protective factors in black). Postpartum haemorrhage, PPH; body mass index, BMI; Caesarean section, CS; antepartum haemorrhage, APH; intramuscular, IM.



8.4 Risk pathways for PPH from ≥500 ml to ≥1500 ml

All women who bled at least 500 ml (n=1302) were included in further multiple regression models identifying the chronological factors for progression to PPH ≥1500 ml. Table 8.3 shows that different variables in different sequential groups and subgroups are associated with progression to severe PPH.

Clinically or statistically significant factors were: Group A) Pre-pregnancy; IMD category education, skills and training (OR 1.75, 95% CI 1.11 to 2.74, p=0.015); BMI (OR 1.03, 95% CI 1.00 to 1.05, p=0.022); previous PPH (OR 1.79, 95% CI 1.06 to 3.02, p=0.030); multiparity with no previous CS (OR 1.65, 95% CI 1.20 to 2.28, p=0.002). Cigarette smoking at first antenatal appointment was negatively associated with progression (OR 0.59, 95% CI 0.36 to 0.97, p=0.039).

Group B, With the addition of current pregnancy health and events factors maintaining statistical significance were: IMD category 'education, skills and training' (OR 1.84, 95% CI 1.16 to 2.92, p=0.009); BMI (OR 1.03, 95% CI 1.00 to 1.05, p=0.023); previous PPH (OR 1.93, 95% CI 1.13 to 3.31, p=0.016); multiparous with no previous CS (OR 1.55, 95% CI 1.12 to 2.16, p=0.009). Maternal smoking remained negatively associated (OR 0.56, 95% CI 0.33 to 0.93, p=0.026). Multiparity with previous CS became negatively associated with progression to ≥1500 ml (OR 0.63, 95% CI 0.43 to 0.92, p=0.0018). Of the newly added variables, those significantly associated with PPH ≥1500 ml were: multiple pregnancy (OR 2.00, 95% CI 1.05 to 3.82, p=0.035) and steroids for fetal reasons (OR 2.00, 95% CI 1.24 to 3.22, p=0.004).

Group C) when intrapartum variables were added those variables maintaining statistical significance were: IMD category 'education and skills' (OR 1.82, 95% CI 1.10 to 3.00,p=0.019); BMI (OR 1.04, 95% CI 1.01 to 1.06, p=0.008); previous PPH (OR 2.39, 95% CI 1.33 to 4.28, p=0.003); multiple pregnancy (OR 2.60, 95% CI 1.27 to 5.38, p=0.009) and steroids for fetal reasons (OR 2.00, 95% CI 1.17 to 3.41, p=0.011). Anterior placenta praevia became statistically significant (OR 5.55, 95% CI 1.29 to 23.9, p=0.022). Smoking became statistically insignificant in the final model. Newly added variables were: physiological management of the third stage of labour (OR 3.74, 95% CI 1.72 to 8.10, p=0.001) and negatively association variables were; unknown interval to suturing of genital tract trauma (OR 0.44, 95% CI 0.25 to 0.79, p=0.006); elective CS (OR 0.14, 95% CI 0.04 to 0.46, p=0.001) and emergency CS (OR 0.34, 95% CI 1.72 to 8.10, p=0.013). These results are graphically represented in Figure 8.3

Table 8.3: Risk pathways for postpartum haemorrhage (PPH) from ≥500 to ≥1500 ml according to chronological variables grouped as pre-pregnancy, during pregnancy, labour and birth. Full regression model: result of three multiple regression models selecting the principal significant variables. In each model, a new additional group of predictors is used. Results are adjusted for other members of the same group and for previous groups only. Women with estimated blood loss (EBL) <500 ml are excluded.

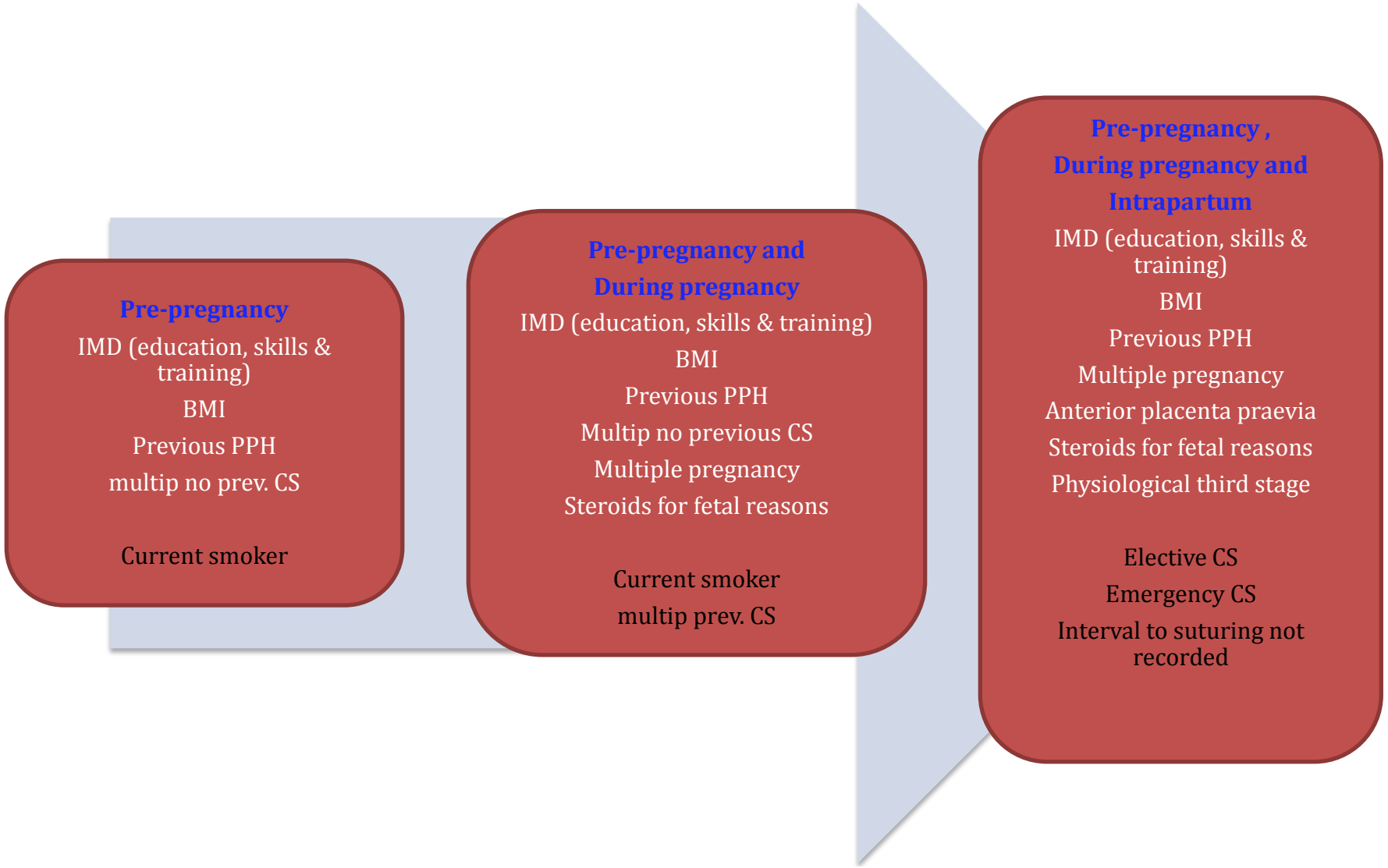
Risk factors included in final model (1230 women included; 70 excluded due to missing data in addition to all women with EBL<500 ml)	**Pre-Pregnancy** Variable subgroups 1-4 **OR (95% CI), p**	**During Pregnancy** Variable subgroups 1-10 **OR (95% CI), p**	**Labour and Birth** Variable subgroups 1- 16 **OR (95% CI), p**
1) **Sociodemographic**			
Age, for each 10 years	0.85 (0.67 to 1.07), 0.16	0.90 (0.68 to 1.09), 0.20	0.99 (0.77 to 1.29), 0.96
Black African	0.86 (0.62 to 1.19), 0.36	0.84 (0.61 to 1.17), 0.31	0.91 (0.64 to 1.30), 0.61
2) **Local Deprivation: Index of multiple deprivation, most deprived UK quintile (%)**			
Barriers to housing and services	0.79 (0.60 to 1.03), 0.076	0.78 (0.59 to 1.02), 0.069	0.75 (0.56 to 1.01), 0.055
Education, skills and training	**1.75 (1.11 to 2.74), 0.015**	**1.84 (1.16 to 2.92), 0.009**	**1.82 (1.10 to 3.00), 0.019**
3) **General and medical risk factors**			
Current smoker	**0.59 (0.36 to 0.97), 0.039**	**0.56 (0.33 to 0.93), 0.026**	0.67 (0.38 to 1.17), 0.16
BMI (kg/m^2)	**1.03 (1.00 to 1.05), 0.022**	**1.03 (1.00 to 1.05), 0.023**	**1.04 (1.01 to 1.06), 0.008**
Assisted conception	**1.41 (0.79 to 2.50), 0.025**	1.02 (0.53 to 1.93), 0.096	1.18 (0.60 to 2.35), 0.64
4) **Previous Obstetric history**			
Previous PPH	**1.79 (1.06 to 3.02), 0.030**	**1.93 (1.13 to 3.31), 0.016**	**2.39 (1.33 to 4.28), 0.003**
Multiparous previous Caesarean	0.70 (0.49 to 1.01), 0.055	**0.63 (0.43 to 0.92), 0.018**	0.84 (0.54 to 1.30), 0.43
Multiparous no previous Caesarean	**1.65 (1.20 to 2.28), 0.002**	**1.55 (1.12 to 2.16), 0.009**	1.17 (0.80 to 1.74), 0.42
5) **Current Pregnancy**			
Multiple pregnancy		**2.00 (1.05 to 3.82), 0.035**	**2.60 (1.27 to 5.38), 0.009**
Admissions >24 weeks		0.67 (0.44 to 1.02), 0.062	0.83 (0.53 to 1.32), 0.43
6) **Antenatal Day Unit (ADU) attendances**			
Any ADU attendance		1.17 (0.89 to 1.56), 0.26	1.05 (0.77 to 1.43), 0.75
PET screen		0.93 (0.55 to 1.57), 0.80	1.15 (0.66 to 2.01), 0.62
Generally unwell		1.49 (0.82 to 2.70), 0.19	1.69 (0.90 to 3.20), 0.11
7) **Placenta praevia**			
Anterior		3.37 (0.86 to 13.30), 0.082	**5.55 (1.29 to 23.9), 0.022**
Major		0.72 (0.17 to 3.05), 0.660	0.97 (0.22 to 4.25), 0.97
8) **Antepartum haemorrhage (APH) & urinary tract infection (UTI)**			
APH		1.26 (0.67 to 2.37), 0.48	1.25 (0.62 to 2.52), 0.53
'Warning APH'		1.70 (0.56 to 5.20), 0.35	1.99 (0.58 to 6.81), 0.27

9) **Pre-eclampsia (PET) and anaemia**			
Gestational hypertension		1.00 (0.47 to 2.16), 0.99	0.98 (0.43 to 2.22), 0.97
Pre-eclampsia		1.03 (0.43 to 2.50), 0.95	0.87 (0.32 to 2.13), 0.69
10) **Medications in pregnancy pre-birth**			
Antibiotics		1.02 (0.74 to 1.40), 0.91	0.95 (0.65 to 1.39), 0.79
Antihypertensives (Incl. for PET)		0.99 (0.56 to 1.78), 0.92	0.91 (0.49 to 1.70), 0.77
Diabetic treatments		0.98 (0.44 to 2.18), 0.96	1.23 (0.52 to 2.91), 0.64
Steroids for fetal reasons		**2.00 (1.24 to 3.22), 0.004**	**2.00 (1.17 to 3.41), 0.011**
11) **Gestation at birth**			
Gestation at delivery (weeks)			0.95 (0.86 to 1.04), 0.25
12) **Birth weight**			
Maximum birth weight (kg)			1.17 (0.87 to 1.59), 0.30
13) **Onset of labour**			
No labour onset			1.28 (0.54 to 3.03), 0.58
Induction			1.07 (0.56 to 2.04), 0.83
Augmentation			1.37 (0.73 to 2.58), 0.33
ROM >2 hours before onset			1.01 (0.60 to 1.70), 0.96
ROM >6 hours before onset			1.16 (0.73 to 1.85), 0.52
ROM unknown			0.95 (0.52 to 1.73), 0.86
14) I**ntrapartum**			
Dinoprostone (Prostin E2®)			1.12 (0.60 to 2.11), 0.73
Oxytocin (Syntocinon®)			0.75 (0.49 to 1.13), 0.17
Spinal anaesthesia			0.73 (0.45 to 1.18), 0.20
Epidural analgesia			1.20 (0.78 to 1.85), 0.41
Temperature, per degree >37.0°C			1.21 (0.75 to 1.94), 0.44
Temperature not recorded			1.40 (0.86 to 2.27), 0.17
Chorioamnionitis			2.70 (0.70 to 10.5), 0.15
15) **Birth**			
Instrumental vaginal			0.79 (0.49 to 1.29), 0.36
Elective Caesarean			**0.14 (0.04 to 0.46), 0.001**
Emergency Caesarean section			**0.34 (0.15 to 0.80), 0.013**
16) **Third stage**			
Physiological			**3.74 (1.72 to 8.10), 0.001**
Ergometrine Maleate/Oxytocin Syntometrine® IM			1.12 (0.66 to 1.91), 0.68
Oxytoxin (Syntocinon®) IV bolus			1.35 (0.63 to 2.87), 0.44

Oxytocinon (Syntocinon®) 40/50 IU commenced			0.97 (0.65 to 1.44), 0.87
Retained placenta			1.40 (0.77 to 2.54), 0.27
Suture interval after vaginal birth (h)			1.16 (0.99 to 1.35), 0.058
Suture interval not recorded			**0.44 (0.25 to 0.79), 0.006**

Full regression model: result of three multiple regression models selecting the principal significant variables. In each model, a new additional group of predictors is used. Results are adjusted for other members of the same group and for previous groups only
Rupture of membranes, ROM; intramuscular, IM; intravenous, IV.

Figure 8.3: Diagram of multiple logistic regression and chronological regression analysis showing predictors of PPH ≥500 ml to ≥1500 ml
(Risk factors in white, protective factors in black). Index of multiple deprivation, IMD; postpartum haemorrhage, PPH; body mass index, BMI; Caesarean section, CS.



8.5 Summary

These hierarchical regression models show that the factors associated with PPH ≥500 ml and ≥1000 ml and progression to ≥1500 ml are different, and all three models provide additional information to that obtained in the previous research.

Initial risk factors for PPH ≥500 ml appear to be superseded by intrapartum events, with only Black African ethnicity and previous PPH remaining statistlcally significant in the final model. Consequently there were no modifiable pre-pregnancy risk factors that could ameliorate blood loss, but this information could prove valuable when women make decisions re place of birth, for example.

Pregnancy health and events that are statistically significant when added to the model for PPH ≥500ml, with the exception of placenta praevia, were over ridden by intrapartum events.

Intrapartum factors that may be modifiable are maximum birth weight, and this could be a surrogate marker for maternal obesity or diabetes, both of which are associated with increased fetal size (Poston, 2012; Heslehurst *et al.*, 2010;). The association of maternal temperature in labour has hitherto not been reported. All medical interventions (induction/augmentation of labour, instrumental vaginal birth and elective or emergency CS) were associated with increased risk of PPH ≥500 ml. In these data Ergometrine Maleate/Oxytocin (Syntometrine®) IM and Syntocinon® 40/50 IU prevented blood loss exceeding 500 ml.

The risk pathway for PPH ≥1000 ml showed that pre-pregnancy factors Black African ethnicity, maternal BMI and previous PPH remained independently associated with estimated blood loss exceeding 1000 ml despite the hierarchical

addition of pregnancy and intrapartum acquired risk factors. Similarly the negative association with smoking at initial antenatal contact remained. The perfect predictive value of anterior placenta praevia is consistent, if unsurprising. The identification of attendance for "generally unwell" is novel. The association of IMD- education, skills and training achieved in the third regression model, although not significant at inclusion is likely to be spurious but requires further investigation.

The risk pathway for progression from 500 ml to severe PPH ≥1500 ml identified yet more risk factors pre-pregnancy IMD 'education and skills' was new. Factors associated with other levels of blood loss were: BMI, previous PPH and multiparity with no previous CS. Pregnancy health and events associated with severe blood loss included multiple pregnancy and anterior placenta praevia. The association with administration of fetal steroids is new, and requires additional investigation.

The identification of both elective and emergency CS as negatively associated with severe PPH, suggests the presence of the multidisciplinary team to react promptly to emergencies, or causes of haemorrhage being essentially different in vaginal and abdominal births. These data suggest different physiological processes are responsible for PPH ≥500 ml, ≥1000 ml and progression to ≥1500 ml.

The findings of these, and earlier analyses, are discussed in Chapter 9.

Chapter 9: Discussion

9.1 Introduction

This thesis addresses several major unresolved issues related to the assessment of blood loss following childbirth. It highlights the limitations of visual assessment of blood loss following birth and focuses on further inaccuracies incurred within reporting and documentation of the incidence of PPH. Furthermore relevant contemporary risk factors are identified through a detailed analysis of PPH prospectively in two large hospital populations over one year (2008-2009). The incidences of PPH and severe PPH reported in this thesis are, to my knowledge, the highest reported from any high-income country (Kramer *et al*., 2013; Lutomski *et al*., 2012; Hogan *et al.*, 2010; Callaghan *et al*., 2010; Knight *et al*., 2009; Khan *et al*., 2006; Cameron *et al*., 2006). The novel application of a weighted sampling strategy in health science highlighted the potential for errors to be introduced between clinical notes and electronic summary data. Additionally digit and threshold preference and avoidance were demonstrated at all levels of blood loss. Day of the week and time of day of birth did not impact on PPH rates for any mode of birth. Established and novel risk factors for PPH at different thresholds (≥500 ml, ≥1000 ml, ≥1500 ml) have been quantified and rigorous and chronological assessment of contributory factors illuminated the complex multifactorial origin of recent rises in PPH.

9.2 Incidence

The main objective of this thesis was to determine the incidence of PPH in the selected cohort and identify the important risks factors leading to blood loss. Women giving birth in the UK are rarely compromised by losing 500 ml of blood, so it was appropriate to focus on more severe blood loss, where maternal morbidities were more likely to occur. Due to variable definitions of severe blood loss, analyses for different categories of blood loss were undertaken (≥500 ml; ≥1000 ml; ≥1500 ml; ≥2500 ml). This was to facilitate comparison with the work of others and uniquely identify the factors associated with minor, moderate and severe PPH. The incidence of overall PPH (≥500 ml) in the current study was 33.9%, which was significantly higher than that reported in the literature (1-10%) at the time of starting the study (Ford *et al*., 2007b; Winter *et al*., 2007; Cameron *et al*., 2006; Wen *et al.*, 2005) or indeed reported since (4-15%) (Euro-Peristat Project, 2013 Bonnet *et al*., 2013; Lutomski *et al*., 2012; Callaghan *et al.,* 2010; Liu *et al*., 2010 Roberts *et al*., 2009). It could be assumed the high rate reported here might, at least in part, be due to inclusion of estimated blood loss following all modes of birth. A recent report from Ireland, also considering all modes of birth and atonic PPH reported a rate of 25.5% (Lutomski *et al*., 2012). With inclusion of all other causes of PPH, it is plausible that these authors would have reported similar rates to the current study.

Further comparison with Lutomski's data demonstrated higher rates of PPH ≥500 ml in the current study following spontaneous vaginal birth and instrumental vaginal birth; 14.8% vs. 4.3% and 41.8% versus 10.1%, respectively (Lutomski *et al*., 2012). Thus high PPH rates in the current study may not be solely attributable to rising CS rates as may be initially assumed.

In Australia and USA blood loss is considered excessive at higher volumes following CS (Ford *et al*., 2007b; Wen, 2005). In the UK, PPH is defined as blood loss exceeding 500ml, regardless of mode of birth. Mean blood loss following CS is indisputably higher than after vaginal birth and with increasing CS rates consideration of increasing the volume to describe excessive blood loss following this procedure may need reviewing.

In the current study PPH rates were also higher at different thresholds, ≥1000 ml 9.4%; ≥1500 ml 4.0%; ≥2000 ml 2.0%; ≥2500 ml 0.8%. Almost 1:5 women lost at least 1000 ml following SVD (4.75% [95%CI 0.37 to 5.7]). When comparing all vaginal births (SVD, forceps, ventouse and assisted breech) with abdominal birth (elective and emergency CS) the rate of PPH ≥1000 ml was 6.1% (95%CI 5.2 to 7.1) versus 18.2% (95%CI 15.8 to 20.7) respectively. Figure 9.1 shows pilot results from the Maternity Safety Thermometer (09/07/2014), a tool currently being developed to measure maternity care outcomes from the woman's perspective. Survey data are collected and monthly reports developed. Most recently the rate of PPH ≥1000 ml was reported as 6.3%, although, when considering term births only, this increased to 7.7%, which is comparable to the current study (www.safetythermometer.nhs.uk).

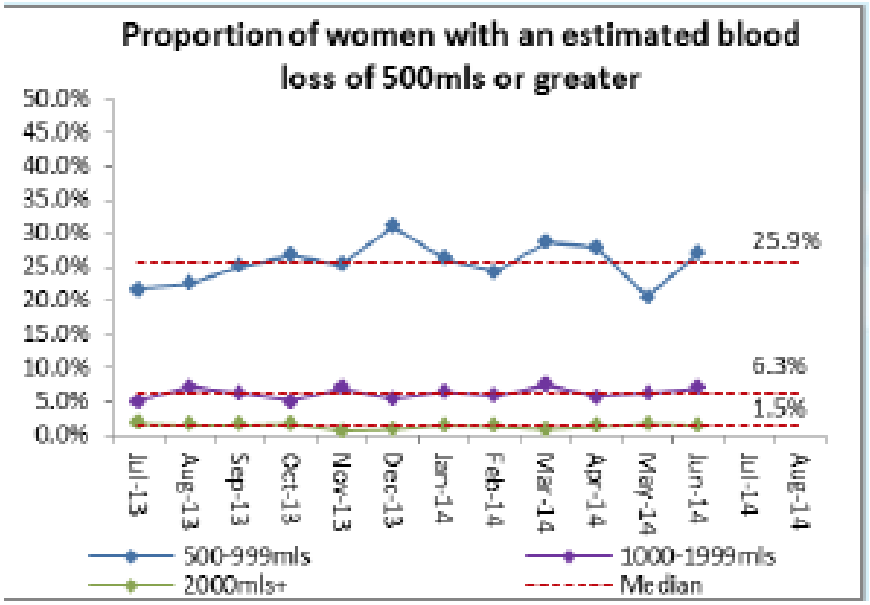


Figure 9.1: The proportion of women with EBL ≥500 ml, by blood loss volume (Maternity Safety Thermometer Pilot Data Report 09/07/2014 p10).

The Maternity safety Thermometer reports rates of PPH≥500 ml as 25.9% and ≥2000 ml as 1.5%. Unlike the current study, these authors failed to demonstrate differences in blood loss according to mode of birth, probably because of the selected denominator used (all women). These findings are shown in Figure 9.2.

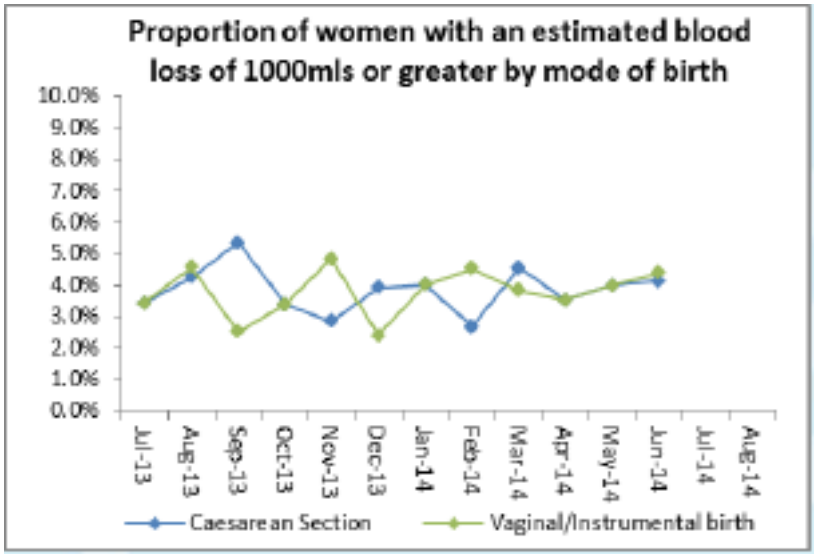


Figure 9.2: The proportion of women with EBL ≥1000 ml by mode of birth using all women surveyed each month as the denominator (Maternity Safety Thermometer Pilot Data Report 09/07/2014 p10)

Recent reports of rising rates (Kramer *et al*., 2013; Driessen *et al*., 2011; Knight *et al*., 2009; Ford *et al*., 2007), up to 13% in high income countries (Mehrabadi *et al*., 2012; Rossen *et al*., 2010) and 15.2% across Europe (Euro-Peristat Project, 2013) may be underestimates, as most studies use routinely collected, retrospective and 'coded' electronic data (Lutomski *et al*., 2012; Kramer *et al.*, 2011; Dreissen *et al*., 2011; Knight *et al*., 2009; Roberts *et al*., 2009; Ford *et al*., 2007; Winter *et al.*, 2007) with inherent errors (Feied *et al*., 2004) and variable data quality (Abrahams and Davey, 2002). Comparison with the Scottish Audit data, which uses risk reports from participating units, demonstrated that the most severe PPHs (>2500 ml) found in my study, although slightly higher, were comparable with this contemporaneous cohort (0.80% versus 0.55%) (Lennox and Marr, 2011) and recent data from the Maternity Safety Thermometer report incidence of blood loss exceeding 2000 ml of 1.5% also suggests the incidence of these highest levels of blood loss in my study are consistent with current trends.

The difference between incidences of PPH at a threshold (≥) compared to a volume above it (>), demonstrated digit preference that was apparent at all levels (≥500 ml, 33.9%; >500 ml 27.8%: ≥1000 ml 9.4%; >1000 ml 7.9%: ≥1500 ml, 4.0%; >1500 ml, 3.3%: ≥2000 ml 2.0%; >2000 ml 1.4%: >2500 ml, 0.8%; >2500 ml 0.6%). This was particularly apparent in PPH 500-999 ml, potentially influenced by Caesarean births with 500 ml blood loss documented. Neither Centre defined PPH as 750 ml or 1000 ml following CS (Fawcus and Moody, 2013: Magann *et al*., 2006). The same phenomenon (blood loss reported at a threshold) is apparent in the severest PPHs, when blood loss should be measured, not visually assessed. It could be assumed that clinicians round up total blood loss, therefore over estimating at this level, however, re-categorisation of blood loss following notes review, suggested this was not the case. Thus confirming a tendency to under estimate at all levels (Al Kadri *et al*., 2011; Kavle *et al*., 2006).

The considerably higher level of PPH in the current study population, therefore, is probably due, at least in part, to the rigorous data collection and validation methodology used. Although the limitations of visual assessment, most commonly used, are well documented and were not overcome in the current study, review of the documented blood loss is justified, as this represents the formal record of pregnancy, birth and the postnatal period (NMC, 2012).

Table 9.1 summarises PPH rates from some recent studies, the majority are calculated using routinely collected clinical data. Furthermore Figure 9.3

demonstrates the temporal rise in severe PPH identified by Kramer and colleagues (2013) but contradicted by a Norwegian study that reported static incidence of severe PPH (Rossen *et al.,* 2010). The Scottish Confidential Audit using data from 2010, 2011 and 2012 has reported a year on year increase in major obstetric haemorrhage since the current study was undertaken, 0.55%, 0.58%, and 0.67% (Lennox and Marr, 2011; Lennox and Marr, 2012; Lennox and Marr, 2013) and a significant increase since the audit introduction in 2004 (Brace *et al*., 2004).

Table 9.1: PPH rates reported in recent studies.

Author	Country	Methodology	Population	PPH definition	PPH rate
Lutomski *et al.,* 2012	Ireland	Hospital In-Patient Enquiry database	Dublin maternity services All risk	Clinician defined according to local protocol, generally >500 ml and diagnosed as atonic	25.5%
Kramer *et al*., 2013	USA	Healthcare Cost & Utilisation Project Nationwide Inpatient Sample 1998-2008	International Classification od Disease codes (ICD-9-CM and subcategories	ICD-9-CM codes 666.0, 666.1, 666.2, 666.3, 990, 990.3, 990.4, 683.9, 684, 689, 755, (severe PPH)	Total severe PPH 4.2 per 1000 Severe Atonic PPH 2.8 per 1000
Driessen *et al.*, 2011	New Zealand	France	Pitagore6 trial database & population	> 500ml or haemoglobin fall of 2 g/dl	20.9%
Mehrabadi *et al*., 2012	Canada-British Columbia	British Columbia Perinatal Data Registry	All women	≥ 500 ml following vaginal birth ≥1000 ml after CS identified by ICD codes	All 8.0% (27% increase since 2000) Atonic PPH 6.4% (33% increase)
Onwere *et al*., 2011	UK	Hospital episode statistics (coded data)	Elective CS for placenta praevia.	No volume defined for PPH	17.5%

EuroPeristat, 2013	Europe	EuroPeristat project national enquiry	All women	ICD codes and local coded data	15.3% (13.7%in previous report)
Dupont *et al.*, 2014	Rhone-Alpes, France	Observational study, clinical audit meetings	Vaginal births	1500 ml, blood transfusion, surgery, radiologic embolization, ITU admission death due to PPH	0.64%
Lennox and Marr 2013	Scotland	National Audit	All women	>2.5l, ≥ 5u transfusion, ITU admission	0.67%
Rossen *et al.*, 2010	Norway	Retrospective electronic records review	All women	> 1000 ml	3.3%

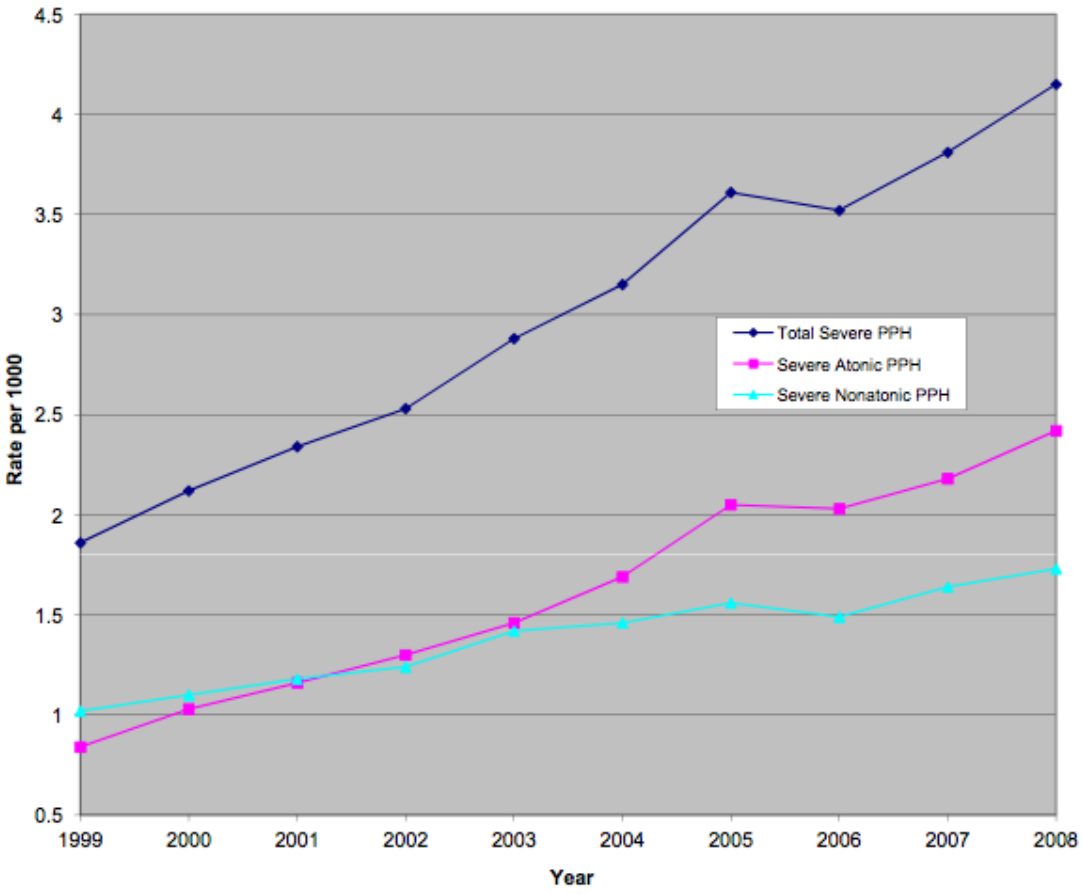


Figure 9.3: Temporal trend in total severe PPH, and clinical subtypes: atonic and non-atonic (from Kramer *et al.*, 2013, p. 1.e3)

There were no PPH related deaths in the study population, confirming that whilst PPH remains a major cause of maternal death in low resource settings (Hogan *et*

al., 2010) it is too rare an event to assess quality of care in high resource countries. Evidence of PPH related morbidities were similar to those reported elsewhere in Europe and the UK during the time frame of the study (Bouvier-Colle *et al*., 2012; Lutomski *et al*., 2012; Weeks, 2008; Knight *et al*., 2007). In the earlier work in the South of England, including the units involved in the current study, the overall incidence of severe obstetric morbidity was 12.0 per 1000 births (95%CI 11.2 to 13.2) and for severe haemorrhage (>1500 ml) was 3.9 (95%CI 3.3 to 4.5) (Waterstone *et al.,* 2001). Thus, in comparison, the current study reports an increase in associated maternal morbidity.

Overall 3.9% of the study population received a blood transfusion. This compares with 7.5% of women with PPH in France (Bonnet *et al.,* 2012), 2.27% in Finland (Jakobsson *et al*., 2012), 16.5% in Ireland (Lutomski *et al*., 2012), 14.3% in Germany and 0.7% in Malta (Euro-Peristat Project, 2013). Reports have suggested that, despite guidelines to the contrary, women with low Hb and following PPH are not readily transfused (Bonnet *et al*., 2012). Confirming this, Lutomski and colleagues (2012) reported an overall increase in blood useage between 1999 and 2009 as shown in Figure 9.4. However this equates to transfusion rates of 0.5 to 1.3%. In the same time period PPH rates increased, however the number of women transfused for atonic PPH, has not increased proportionally (17.6% in 1999; 16.5% in 2009) as shown in Figure 9.5 (Lutomski *et al*., 2010).

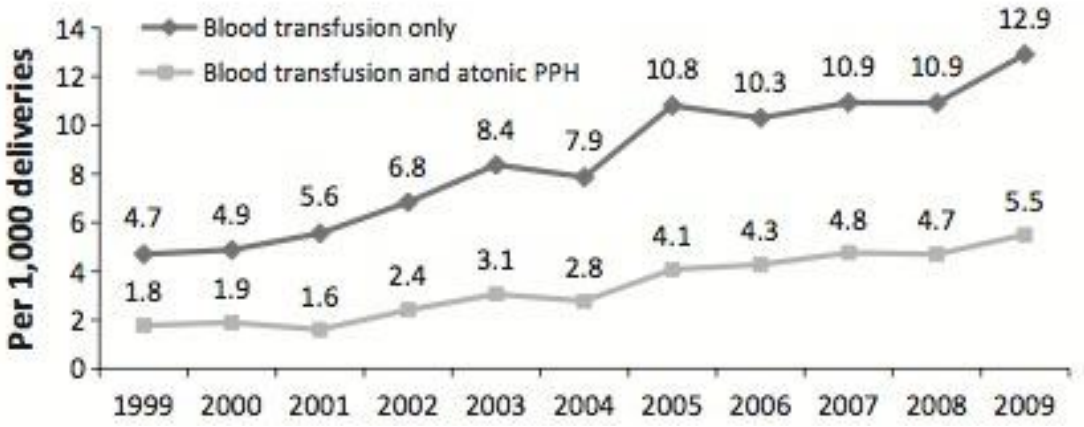


Figure 9.4: Blood transfusion rates and blood transfusion rates as treatment for atomic PPH in Ireland 1999-2009 (Lutomski et al., 2012, p310)

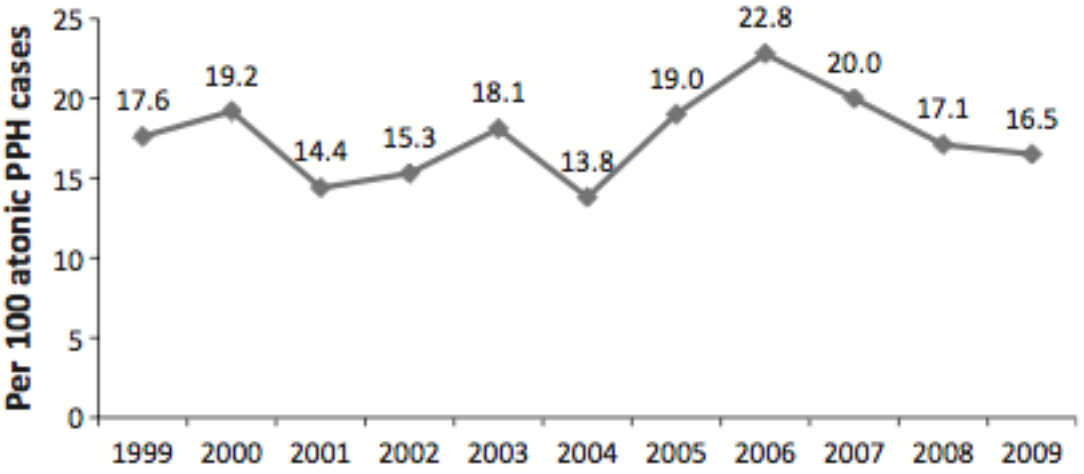


Figure 9.5 Blood transfusion rates for treatment of atonic PPH 1999-2009 in Ireland (Lutomski *et al*., 2012, p310)

Both units had access to blood and blood products, yet 12 women received O rhesus D negative blood (universal donor), indicating that despite advances in the processes of cross matching and improved accessibility of cross matched blood, the availability of emergency obstetric blood remains an integral part of management of PPH.

Other blood products were utilised sparingly with minimal use of cryoprecipitate in both Centres and no fibrinogen used in Centre 2. Recent innovations in transfusion therapy suggest correction of coagulopathies may effectively reduce overall transfusion rates (Spahn and Rossaint, 2005; Moor *et al.,* 2009; Moore and Chandrahan, 2010).

The development of hypofibrinogenaemia and resultant impaired haemostasis has been identified as problematic in PPH (Fenger-Eriksen *et al*., 2008). Currently there are several randomised trials ongoing to investigate early treatment with fibrinogen, including the FIB-PPH trial (Denmark) NCT01359878 (Wikkelsoe *et al.,* 2012) and OBS2 (Wales) ISRCTN46295339 (Collins, *et al.*, personal communication). In the current study the influence of coagulopathies could not be assessed.

Autologous transfusion in obstetrics, although reported as early as the 1990s (O'Dwyer *et al*., 1993), was not widely employed at the time of this study (Geoghegan *et al.,* 2009). There was no system available in Centre 1 and it was only used in one case of antenatally diagnosed placenta percreta in Centre 2. It is plausible that, should the study be repeated, transfusion practices may have altered further with more women receiving autologous transfusions.

The incidence of manual removal of placenta was in line with reports by others (Weeks, 2008). Delay in delivery of the placenta has been described as a modifiable risk factor in the prevention of PPH (Winter *et al.,* 2007). Despite this, wide variation in practice and timing has been noted (Deneux-Tharaux *et al*.,

2009). Overall, duration of the third stage is considered important to reduce PPH; despite variation in timing (EUPHRATES collaborative group, 2005) general consensus being failure to deliver the placenta within 30 minutes of the baby's birth increases blood loss (Combs *et al*., 1991), with Magann and colleagues proposing 18 minutes as the optimal time (Magann *et al*., 2005). A further RCT, abandoned due to imbalance in the arms caused by placental delivery within 20 minutes, suggested that a third stage exceeding 10 minutes was associated with PPH, but caution should be heeded as this time frame was not a pre-specified endpoint, and 89% (n= 1430) of the placentae delivered within 10 minutes (Magann *et al*., 2006).

The long term effects of haemostatic sutures have been variably reported as influencing future fertility (Sentilhes *et al*., 2010a; Sentilhes *et al*., 2010b) and causing gynaecological problems (Ibrahim *et al*., 2013). It is not possible to assess either the impact of previous haemostatic sutures or the influence of this treatment on subsequent pregnancies within the remit if this study.

Despite being advocated as an effective treatment for PPH, particularly in low-resource settings, concurring with others, balloon tamponade was rarely used in our population (Tindell *et al*., 2013). There is a paucity of evidence regarding the effectiveness of this technique, with early reports limited to case reports (Bakri, 1992; Katesmark *et al.,* 1994; De Loor and van Dam, 1996; Marcovici and Scoccia, 1999) and small retrospective (Keriakos and Mukhopadhyay, 2006) and prospective studies (Condous *et al.,* 2003). More recently a population cohort study found that balloon tamponade was effective at achieving haemostasis and preventing employment of more invasive procedures (Laas *et al*., 2012). A

prospective randomised controlled trial could fully evaluate the effectiveness of this hitherto underused technique, and its impact of subsequent maternal morbidities.

The peripartum hysterectomy rate was slightly higher than the incidence reported in an earlier UK national survey (0.40 per 1000) (Knight, 2007) but less than reported in a more recent UK (0.55 per 1000) and Australian cohort (0.85 per 1000) (Knight, 2010; Awan *et al*., 2011). Other more recent reported rates from local review data include 0.42 per 1000 births in Portugal (Carvalho *et al.,* 2012) and 0.92 per 1000 births in Greece (Christopoulos *et al*., 2011) A systematic review reporting a rate of 0.2 to 5 per 1000 births (Rossi *et al.,* 2010) has been criticised for broad definitions, potentially inflating the rate (Knight *et al*., 2010).

Lutomski and colleagues in Ireland and Parazzini and colleagues in Italy reported temporal increases in maternal morbidities, especially associated with PPH (Lutomski *et al*, 2012; Parazzini *et al*., 2013). The Scottish audit of severe maternal morbidity has similarly reported increased maternal morbidities associated with PPH since the inception of the Reports in 2004. These data comfirm the impact of PPH on short and long term associated morbidities for women and their families.

The data management system enabled "real time" importation of electronic summary data from NHS databases, facilitating immediate identification of cases and rapid review of patient records. Additionally importation of uploaded clinical data incurred no impact for clinical staff, and evaded further errors incurred by

duplication (Hammond, 2003). To our knowledge, no similar system exists for monitoring and auditing PPH. Many studies, as mentioned previously, have relied on routinely entered and coded data and surrogate markers for PPH which was not validated. So comparison with these studies is not particularly informative. More useful, is the study by Roberts *et al.* (2009) which actually reviewed a series of 1200 randomly selected women in Australia and reported an incidence of PPH of 11.4% which the authors considered an under estimation. This is obviously still lower than the incidence in the current study, and could be explained by the use of the weighted sampling strategy. This much more robust approach identified women with all levels of blood loss for review, rather than the random selection employed in the Australian study, which may have omitted or under-represented some categories. Additionally, the PPH incidence in the Robert's study was also further underestimated because the definition for PPH at CS in Australia was 750 ml rather than 500 ml (Roberts *et al.,* 2009).

9.3 Methodology employed

The identification of cases from routinely data collection conveyed no burden to clinical staff. The weighted sampling strategy overcame many of the issues highlighted in the literature above, and addressed the limitations of case control studies, which are generally smaller and may focus on a restricted range of blood loss. Extraction of data from a complete cohort combined with a weighted strategy facilitated random identification of a large number of women with all categories of estimated blood loss. The weighted sample ensured that, whilst most cases reviewed were those of maximum interest (largest estimated blood loss) a representative sample of all other estimated blood loss volumes was also reviewed. The acquisition and review of all available records for selected women meant that blood loss was identified for all women in the sample, and all levels of

estimated blood loss. The additional identification of all women who received blood or blood products meant 35 women, with lower estimated blood loss volumes recorded and not randomly selected, underwent detailed review.

Based on this, and using the error rates identified in routinely collected electronic summary data, employment of this methodology could be recommended as it provides an effective tool for contemporaneous monitoring of PPH locally, regionally and nationally and could be further modified and extrapolated to monitor other morbidities.

9.4 Effect of time of birth

There were no significant differences between PPH rates by day of the week or time of day for all modes of birth, including elective CS. This differs from evidence on other elective surgical procedures (Aylin *et al*., 2013) and may be the result of the '24/7' Consultant presence on labour wards advocated in the Confidential Enquiry into Maternal Deaths and aspired to in both participating Centres (Lewis, 2007b). It was notable that some elective procedures were undertaken 'out of hours'. This could be due to labour ward staffing levels and policies, or errors in classification of urgency of CS (Wickham, 2010) and availability of specialist neonatal cots (Centre 1 is the regional referral Centre for babies with cardiac conditions). Further investigation showed some consultants delivered private patients in NHS facilities during weekends on call. Thus ensuring they were available for these patients and accounting for some 'out of hours' elective work. The safety of this practice remains questionable, with resultant implications for workforce workload.

9.5 Reporting errors

This study also allowed for the comparison of NHS electronic summary data with documented blood loss in hand held maternity records. This provided quantifiable data describing the errors generated during routine transcription from paper to electronic clinical databases. There is literature about errors related to blood loss estimation (Al Kadri *et al.,* 2011; Buckland *et al.,* 2007; Bose *et al.,* 2006; Larsson *et al.,* 2006; Glover, 2006), but currently, there has been little emphasis on the additional human error introduced by the need to replicate paper records electronically (Fawdry *et al*., 2011). In the current study, this process introduced a 0.19 to 2.03% error rate when transcribing basic data (e.g. maternal date of birth, time of birth of baby, mode of birth, birth weight and sex of baby), but worryingly introduced a 13.6% (14.9% in Centre 1 and 12.3% in Centre 2) error rate when entering blood loss information. The underlying reasons identified included failure to update electronic records when subsequent bleeding occurred in the first 24 h postpartum and incorrect addition of volumes recorded in hand held notes. These issues could easily be addressed by requiring ongoing addition of blood loss on each page of the handheld postnatal notes and inclusion of a data field regarding subsequent blood loss on the electronic discharge summary.

Caution regarding errors introduced by data overload in maternity service has been highlighted previously by Fawdry *et al.* (2011) and the moving to electronic records has been strongly advocated by others in emergency medicine (Feied *et al.,* 2004) and for other aspects of the health service (Freund *et al.*, 2013). The abolition of hand held notes requiring transcription to NHS databases to a direct first entry electronic process could remove sources of transcription error and provide a mechanism for automated data monitoring. However the requisite internet access in addition to appropriate computer hard and software would require significant infrastructural and financial input.

The evidence of digit and threshold preference and avoidance in estimating blood loss is interesting and further investigation is required regarding the factors that influence midwives and other health care professionals when assessing blood loss. Understanding these factors could improve educational packages and ultimately improve the longevity of retention of improved assessment and be included in new strategies to improve patient care (Bingham, 2012).

9.6 Prediction of those at risk of PPH

Identification of women at risk, and resultant prediction, of PPH has long been attempted and is demonstrated by the numerous cited risk factors described in chapter 6. However, further complexity is introduced by the historical and ongoing diversity of definitions used. Some classifications are dependent on blood volumes lost, identified specifically (Lennox and Marr, 2013; Keriakos and Chaudhuri, 2012; RCOG, 2009; WHO, 1990b), alternatively when early postpartum blood loss is considered 'excessive' (NICE, 2007), or requirement for blood product replacement (any, >5 units, >10 units) (Holm *et al.,* 2012; O'Brien *et al.,* 2010; Macphail and Fitzgerald, 2001). All these are further compounded by application of different definitions according to mode of delivery (RCOG, 2009; Naeff *et al.,* 1994). Many identify risk factors for PPH at a specified level, be it any blood loss exceeding 500 ml (Biguzzi *et al.,* 2012; Bibi *et al.,* 2007) more severe haemorrhage (variably defined) (Al-Zirqi *et al.,* 2008), or leading to associated severe morbidity, such as hysterectomy or ITU admission (Knight, 2007). One study investigated PPH at both >500 ml and >1000 ml and relied on retrospective analyses of an electronic data register, but only included low risk women following vaginal birth. These authors noted that 2 women received blood products despite estimated blood loss <500 ml, and, essentially focusing on intrapartum risk factors, concluded retained placenta and third stage duration

>30 minutes were positively associated with PPH ≥500 ml and ≥ 1000 ml (Bais *et al.,* 2004). However these authors had removed all pre-existing or pregnancy acquired risk factors with the exception of ethnicity, but they had categorized this as 'West European' and 'non-West European', so comparison with other reports is problematic.

Another recent study failed to use any blood volume lost to define PPH and severe PPH, rather using the requirement for >1 unit transfusion and >3 unit transfusion (Mehrabadi *et al.,* 2013). This would appear more indicative of blood product availability and transfusion and management protocols than severity of blood loss. Added to which thresholds for transfusions have altered in recent years (Wen *et al.,* 2005) and the widespread availability of cell salvage also reduces total volume replacement requirements (Ashworth and Klein, 2010). Additionally new transfusion regimes developed in military medicine, require validation in obstetrics, but may further alter protocols (Saule and Hawkins, 2012). Thus the employment of transfusion requirements should be considered an unreliable and inconsistent surrogate proxy for severity of PPH.

None of these studies verified the information used with other data sources prior to analyses. Thus the proportion of missing or inaccurate data could not be assessed, which would have undoubtedly impacted on the results. Exceptions being UKOSS reports and the Scottish Audit of Severe Maternal Morbidity which rely on local clinicians completing minimal data reports and may be subject to ascertainment bias (UKOSS, 2013; Lennox and Marr, 2013). In both situations, no validation of the reports was undertaken.

However, the current study undertook detailed review of all available patient records, and triangulated reported details from different data sources, for example documented biochemical information in handheld notes with those available from the results system, cross checked with treatment charts and electronic summary data.

The wealth of data collected in the current study allowed for the both univariate and multivariate regression analysis. This study was designed to assess the independent impact of sequentially attributed confounding factors, which was not possible in studies using coded data or reliant on admission and discharge data. Many risk factors identified as associated with PPH ≥500 ml were not necessarily associated with larger haemorrhages or *vice versa*. This highlighted the need to consider the complex interlinked contributing factors leading to PPH and how they contributed to the progression onto severe PPH. Risk assessment using chronological categories was preferable to stepwise regression, as, each variable within the category and each group of predictors were considered, whilst also adjusting for the influence of predictors identified from previous groups (potential confounders). By fitting new elements singly, factors not significantly related were removed. In this way, adjustments were made for potential confounders at each stage (Hernan *et al.,* 2002). Investigating estimated blood loss at multiple levels, including equal to and more than (≥), and more than (>) thresholds, optimised comparison with other reports, which has not been achieved previously. Using this approach, significant pre-pregnancy risk factors were often superseded by other pregnancy acquired or intrapartum risk factors. Their impact varied according to size of PPH, included age, ethnicity, BMI, previous PPH and assisted conception.

9.6.1 Pre-existing factors predicting PPH

The positive association between PPH and maternal age is variably reported (Lyndon *et al.,* 2012; Montan, 2007; Cameron *et al.,* 2006; Diejomaoh *et al.,* 2006). Older women are reported to have more medical (Dhanjal, 2009) and obstetric co-morbidities (Kenyon and Bewley, 2009) and poorer uterine contractility (Smith *et al.,* 2008). With increased numbers of older women embarking on pregnancy further work is required to more accurately ascertain the risk of PPH in this age group (Euro-Peristat Project, 2013).

Other studies have identified specific ethnicities, namely Hispanic and Asian at increased risk of PPH (Bryant *et al.,* 2012) no previous study has specifically identified Black African ethnicity as an independent predictor (Cabacungan *et al.,* 2012; Bryant *et al.,* 2012; Kramer *et al.,* 2011; Magann *et al.,* 2005; Waterstone *et al.,* 2001), possibly because of lack of adjustment for potential confounding variables (Calvert *et al.,* 2012; Berg *et al.,* 2010; Al-Zirqi *et al.,* 2008; Sundararajan *et al.,* 2007). The sequential addition of risk factors in the current study may account for uterine fibroids being associated with increased blood loss, but not PPH at any level. Women of African American ethnicity have been reported.to be more at risk of pregnancy related death, but not PPH (Harper *et al.,* 2007). In a UK cohort Knight and colleagues (2009) identified non-White women as more at risk severe maternal morbidities, including peripartum hysterectomy. Although overall Black Caribbean women were the most highly represented ethnic minority group, both Black Caribbean and black African women had more than double the risk of severe maternal morbidity than White women. This concurs with others regarding outcomes for non-indigenous women (Callagan *et al*., 2008; Zwart *et al*., 2008). Some reports have suggested that migration history

may be important in assessing longer term health and risk factors of immigrants and the health of subsequent generations (Giuntellaelli, 2012; Jayaweera, 2011). These data are rarely collected, but may be beneficial in assessing long term health of multiethnic communities and to inform public health initiatives.

The positive association between BMI and PPH concurs with findings for prospective cohort studies (Fyfe *et al.,* 2012; Raja *et al.,* 2012; Blomberg, 2011) although retrospective and routine data reports are equivocal (Paglia *et al.,* 2012; Sebire *et al.,* 2001a; Sebire *et al.,* 2001b). At first glance the impact of BMI appeared modest, but this 4% increase per BMI unit became substantial in higher obesity categories.

The newly identified positive association with assisted conception could reflect multiple pregnancy or abnormal placentation (RCOG, 2011b; Kallen, 2008). Causes of infertility and assisted conception techniques have been ascribed varying risk profiles (Breheny *et al.,* 2009). In the current study insufficient detail regarding gynaecological history or assisted conception treatment was collected to make comparisons, and further research in required in this area.

With regard to previous obstetric history, these data did not highlight any association with either maternal age or previous caesarean and severe PPH. Contradicting the findings of others with regard to previous CS and association with blood loss exceeding 1500 ml (Al-Zirqi *et al*., 2009). Established pre-index pregnancy risk factors for severe PPH in the general population included maternal age, BMI, multiple pregnancy and previous caesarean (Blomberg, 2011; Arrowsmith *et al*., 2011; Fong *et al*., 2010; Waterstone *et al.*, 2001, Sebire *et al*.,

2001a; Sebire *et al*., 2001b; Coulter-Smith *et al*., 1996). In addition, these data quantified and confirmed the impact of previous PPH on blood loss in a subsequent pregnancy (Driessen *et al*., 2011; Ford *et al.,* 2007). The positive association of grand multiparity with PPH (Driessen *et al.,* 2011: Shahida *et al.,* 2011) could not be validated in the current study due to the low parity of the population, and limited number of women with >4 previous births. Grand and great-grand multiparity may become less important risk factors as family size diminishes (ONS, 2011).

These data concur that multiparity is protective against PPH (≥500 ml) (Ford *et al.,* 2007) using primiparous women as the reference group were at increased risk of PPH. Unexpectedly, this study identified that multiparity without previous CS and one subscale of the index of multiple deprivation (education, skills and training) for England (HM Government, 2012) were risk factors for progression to severe PPH (≥ 1500 ml). These are curious and require further research.

In the present study, smoking was found to be protective against large haemorrhages (≥1500 ml) despite being previously associated with placental abruption (Kitsantas and Christopher, 2013; Tikkanen *et al.,* 2011; Ananth *et al.,* 1996). Both may be a consequence of smoking induced impairment of placentation and endothelial function, abruption being due to poor placental adhesion and the protective effects against severe PPH due to failure of the spiral arteries and other vessels to adapt to pregnancy, restricting uterine blood supply and also associated with fetal intrauterine growth restriction (Zdravkovic *et al.,* 2005; Werler *et al.,* 1997)

9.6.2 Pregnancy- acquired factors predicting PPH

Pregnancy acquired risk factors for PPH confirmed in the multivariate analyses included: multiple pregnancy (Callaghan *et al.,* 2010; Magann *et al.,* 2005), placenta praevia (Kramer *et al.,* 2011; Onwere *et al.,* 2011) pre-eclampsia (Eskild and Vatten, 2009) and macrosomia (Malabarey *et al.,* 2011;Jolley, 2003). The novel association with prelabour antibiotic use could reflect chorioamnionitis, and requires further investigation in light of reported levels of antibiotic use in pregnancy (de Longe *et al.,* 2013). However, two randomised controlled trials of antibiotic use to prevent preterm birth, have not reported blood loss in their outcomes (Shennan *et al.,* 2006; Kenyon *et al.,* 2001).

Similarly, this study confirmed that multiple pregnancy (Kramer *et al.,* 2011) and anterior placenta praevia as predictors of progression to severe PPH ≥1500 ml (Kramer *et al.,* 2011; Watanabe and Matsubara, 2010; Waterstone *et al.,* 2001; Stones *et al.,* 1993). The novel association of PPH with administration of steroids for fetal lung maturation could be linked to multiple pregnancy (a risk factor itself) and threatened preterm birth (Roberts and Dalziel, 2007), although gestation of delivery showed no effect.

Data indicated that over 62% of women with Hb <8.5 g/l had PPH, 26% of whom progressed to severe PPH. This is of interest because NICE guidelines have recently identified this as a threshold for concern and advise treatment (NICE, 2010). The positive associations between third trimester anaemia and severe PPH using higher thresholds (as advised by the Government of South Australia, 2012; and the RCOG, Arulkumaran *et al.,* 2009) were not confirmed by these data.

In the current study there was no association with maternal antidepressant medication in the last week of pregnancy and PPH. This contradicts the findings of a large US study which recently reported a 1.4 to 1.5 fold increased risk of PPH in women taking serotonin and non-serotonin reuptake inhibitors for their depression (Palmsten *et al*., 2013). This may be partly explained by the small numbers of women on these medications immediately prior to giving birth in the current study. Palmsten and colleagues noted that there was no association with these medications and PPH in older women, and this may also be a reason why this result was not apparent in my study. Additionally these authors did not adjust for BMI, which is known to impact on depression (Heslehurst, 2010), or confirm drug compliance at time of birth. However, with increasing reports of antenatal depression further investigation is required regarding these results, in order for clinicians to ensure these women receive the best care possible, and for labour ward staff to be aware of this potential risk factor.

9.6.3 Intrapartum factors predicting PPH

Several important intrapartum risk factors for PPH identified, have been discussed previously in the literature including chorioamnionitis (Malabarey *et al.,* 2011), instrumental and caesarean births (Unterscheider *et al.,* 2011; Sheiner *et al.,* 2005) and retained placenta (Magann *et al.,* 2005). The RCOG Green top guideline for PPH recommends monitoring of maternal temperature in labour (Arulkumaran *et al.,* 2009) but does not specify temperatures of concern. These results strongly suggest that any maternal temperature above 37.2 °C is a risk factor for PPH ≥500 ml and ≥1000 ml, and justifies inclusion as an alert trigger (coloured amber) in some versions of the modified obstetric early warning system (MEOWS) charts advocated by maternal mortality reports (Lewis, 2007). The

linear relationship between blood loss and maternal temperature requires further investigation.

Induction and augmentation of labour were not associated with haemorrhage ≥500 ml in agreement with an earlier report (Stock *et al.,* 2012) but at variance with others (Lutomski *et al.,* 2012; Smith *et al.,* 2008). Further recent evidence suggested that mode of induction of labour may be associated with PPH, defined as estimated blood loss ≥1000 ml and postnatal requirement for blood transfusion (Jozwiak *et al*., 2011). These authors reported induction of labour using a Foley catheter was associated with less PPH than induction with prostaglandins. This was an *a priori* secondary outcome in their open labelled, multicentre RCT in both multiparous and primiparous women. Contradicting the earlier findings of Pennell and colleagues who reported no difference in PPH rates comparing three modes of induction in nulliparous women with unfavourable cervixes (Pennel *et al*., 2009).

Meta analysis of these two studies showed Foley catheter induction was less associated with PPH (OR 0.60 [95%CI 0.37 to 0.95]) (Jozwiak *et al*., 2011). However another meta-analysis of 5 studies investigating the association between induction of labour and CS, with PPH as a maternal secondary outcome, concluded that PPH and induction versus expectant management of onset of labour was not statistically significant (0.78 [95%CI 0.58 to 1.05]) (Wood *et al*., 2014).

Further investigation regarding mode of induction of labour and PPH is required where blood loss is a powered for primary endpoint, as induction and augmentation rates appear to be rising, not least in a bid to reduce CS rates

(Wood *et al*., 2014). Additionally innovative methods of should be explored.

The positive association between elective and emergency CS and retained placenta on risk of PPH, as previously reported in the literature (Fong *et al.,* 2010) Arulkumaran *et al.,* 2009; Weeks, 2008), were notable.

The positive association of oxytocin (Syntocinon®) use in the first and second stage and PPH ≥1000 ml concurs with some previous research (Selo-Ojeme *et al.,* 2011: Rossen *et al.,* 2010). This could be because oxytocin use prior to birth may adversely affect the uterine response to a bolus dose for the third stage. Due to varying oxytocin administration regimes to induce and augment labour, and variation in uterotonic agents employed for third stage management it is difficult to confirm or refute this. However when the effectiveness of pulsatile *versus* continuous, and high dose or low dose, oxytocin was investigated no difference in PPH rates was noted (Tribe *et al.,* 2012; Mori *et al.,* 2011).

Elective and emergency section were both positively associated with PPH ≥500 ml, but negatively associated with progression to severe PPH (AORs 0.14, 95% CI 0.04 to 0.46 and 0.34, 95% CI 0.15 to 0.80). This is likely to be due to prompt surgical and anaesthetic interventions, resource availability and effective protocol adherence (Shields *et al.,* 2011). Emergency CS has previously been positively associated with severe PPH (Holm *et al.,* 2012; Al-Zirqi *et al.,* 2009) and the RCOG state severe PPH is less likely following elective caesarean births (Weston, 2012; Alzirqi *et al.,* 2009).

9.6.4 Third stage intrapartum factors predicting PPH

Prophylactic Ergometrine Maleate/Oxytocin (Syntometrine®) IM and high dose oxytocin (Syntocinon®) IV infusion for management of the third stage were negatively associated with PPH, reinforcing concerns (Rogers, 2011) about current recommendations for oxytocin (Syntocinon®) IM (5-10 units) as appropriate to prevent PPH (NICE, 2007). A national survey suggested Ergometrine Maleate/Oxytocin Syntometrine® IM use remains widespread (Farrar *et al.,* 2010), if this is indeed the case, it contradicts opinion that changes in uterotonic drugs for management of the third stage have contributed to rising PPH rates (Rogers, 2011).

Whilst not positively associated with PPH, physiological management of the third stage was a risk factor for severe PPH ≥1500 ml, possibly related to delays in recognition or treatment, although in a large population study <0.5% postnatal transfers from home or free standing midwife led units were for maternal reasons, however, this was a low risk cohort (Rowe *et al.,* 2012). This finding could also be associated with staff competence in practicing physiological management, given the high incidence of active management in the current study (92.3%). In early randomised controlled trials initial results showed higher rates of PPH in the physiological arm of the studies, but this became less apparent as staff became familiar and competent with physiological management (Rogers *et al.,* 1998; Prendiville *et al.,* 1988).

Systematic reviews of RCTs and quasi-RCTs have consistently shown that active management of the third stage reduces blood loss, but more recently physiological management has been considered a natural conclusion of a normal labour and not been associated with adverse outcomes in women with no risk

factors (Begley *et al*., 2011; Prendiville *et al*., 2003; Prendiville *et al*., 2000). The most recent review commented on the paucity of good quality data in the 7 trials included (n= 8247), however whilst confirming active management did reduce blood loss and was associated with fewer postnatal Hb <9 g/dl, it was not without consequences for mother and baby. Mothers were more likely to experience hypertension, nausea and vomiting and early cord clamping was associated with lower neonatal birthweight. This was attributed to reduced placental perfusion when the cord was prematurely clamped, which could have subsequent sequelae for the health of the child. There was a suggestion that controlled cord traction could lead to fragments of placental tissue being retained causing subsequent readmission. Furthermore the reviewers found no statistically significant difference in incidence of PPH > 1000ml in high resource countries where active management is widely practiced compare to low resource settings where expectant management is the norm (Begley *et al*., 2011). The rigorous review process of RCTs, quasi RCTs and systematic reviews reliably answer investigations comparing one type of treatment with another, or provide evidence for single specified end points. The value of findings from observational studies, such as the current work, is frequently questioned, but this study set out to identify current practices regarding the prediction and management and PPH, and therefore the research questions could not have been addressed by RCT or systematic review methodologies. Even within the constraints described, these observations require further investigation.

Time to complete genital tract repair was confirmed as a risk for PPH (Ozdegirmenci *et al.,* 2010) and where this is not recorded was a risk factor for progression to severe haemorrhage, contradicting the findings of others (Fong *et al.,* 2010).

9.6.5 Summary of associated variables contribution to PPH at all levels

Whilst some variables can be broadly categorised as caused by 1) surgical interventions, for example, assisted conception techniques, previous CS, CS; 2) genital tract trauma, for example, instrumental vaginal birth, macrosomia, tears and episiotomies; or 3) suboptimal contractility, for example Black African ethnicity, maternal age, BMI and previous PPH. However it is unclear which of these categories some of the identified variables would influence, for example, maternal steroid administration for fetal reasons, and maternal temperature in labour.

These data further illuminate the complexity of PPH and the contribution and pathways of the condition. In the final models at each threshold the difference in associated variables indicates the potentially different pathways for different levels of blood loss. This means the concept of progression from minor to major haemorrhage may be intrinsically flawed. This has implications for the commonly held belief that a large haemorrhage may be the result of a poorly managed minor bleed, and reporting mechanisms therefore should be investigative and blame free.

9.7 Associated morbidities

9.7.1 Blood transfusion

Inconsistent blood transfusion policies have been identified as problematic when used as a marker of severity of PPH (Wen *et al*., 2005). In the current study 3.9% of women received a blood transfusion. This compares with 1.98% in

Finland (Jakobson *et al*., 2013), 2.3% and 1.03% in the USA (Alexander *et al*., 2009; Ehrenthal *et al*., 2012) and 0.31% in Canada (Balki *et al.,* 2008). Several authors report higher transfusion rates associated with CS compared with vaginal birth, although rates remain low 0.49% in Canada 0.63% in Australia and not significantly different between elective and emergency procedures (Balki et al., 2008; Chua *et al.,* 2009). Given increasing rates of CS in developed countries it is likely more women will require blood products, although antenatal treatment of haemoglobin levels below 9.5g/dl have been advocated as reducing transfusion requirement following CS and require further assessment (Ehrenthal *et al.,* 2012). A retrospective analysis of maternal deaths caused by PPH in France (n=38) reported availability of blood products in 79% of cases, with 3 women not being transfused (Bonett *et al*., 2011). The availability of O rhesus negative blood is acknowledged as pivotal in the management of severe obstetric haemorrhage. In the current study, despite the availability of rapidly matched blood in both centres, 12 women (0.12%) required resuscitation with O rhesus negative blood, this compares with 278/34734 (0.80%) in a Canadian cohort (Bhella *et al.,* 2012). The rarity of autologous blood transfusion in the current study means comparisons cannot be drawn with other investigations. Increasingly cell salvage is advocated as a useful treatment for women where massive blood loss is anticipated, patients are fully informed regarding the procedure and there is a multidisciplinary team cognisant with the technique (NICE, 2005). However it has been suggested that cell salvage is underused due to considerations regarding inappropriate resource given the unpredictability of severe PPH (Peacock and Clark, 2011).

9.7.2. Surgical treatments to ameliorate blood loss

Expedient repair of genital tract trauma effectively ameliorated blood loss in 152 women (1.52%) in the current study and is therefore identified as a potentially modifiable action to reduce PPH. However the impact of early repair was minimally effective at reducing blood loss due to trauma but did not influence haemoglogin or haematocrit levels in one RCT (Ozdegirmenci *et al*., 2010).

In this cohort 9% of PPH ≥500 ml were treated by insertion of haemostatic suturing. Insertion of haemostatic sutures was first utilized by B-Lynch in 1997 and since that time several modifications have been identified as an effective method of stopping bleeding, whilst preserving fertility. There are no RCTs in the literature comparing sutures, but many advocates of different variations (B-Lynch *et al*, 1997; Cho *et al*., 2000; Hayman *et al*., 2002; Nelson and Birch, 2006). It would appear haemostatic sutures, when properly applied, are effective and ameliorating blood loss.

Other techniques advocated as effective treatment for intractable haemorrhage, such as vaginal packing and balloon tamponade, were minimally employed in the current cohort (n=24 women and m=21 respectively). There is a paucity of RCTs regarding balloon tamponade, and existing case series reports often group and assess all tamponade, thus the effectiveness of one device, over others, is not possible to assess (Georgiou, 2009). Those assessing individual devices, such as the Bakri balloon tend to me small and therefore, although they are reportedly effective in treating PPH, heterogeneity of the research design and differences in practice variation mean generalisability is uncertain (Aibar *et al*., 2013; Vitthala *et al.,* 2009). Further prospective studies investigating and comparing tamponade

devices is required, in the current study it is possible balloon tamponade was an underused treatment.

Interventional radiology, although available on both participating sites and advocated in protocols, was only used on one occasion in the current study. Underuse of this effective treatment has been reported elsewhere (Webster *et al*., 2010). Familiarity with procedures and treatments has been advocated to ensure effective treatment, and the minimal use of interventional radiology could indicate the need for considerable multidisciplinary educational input.

9.7.3 Manual removal of placenta/ placental delivery

Expedient management of the third stage has been advocated as reducing the risk of PPH, indeed Magann and colleagues (2005) considered prolonged third stage occurs 18 minutes after delivery of the baby, and the risk of PPH increased 6-fold when the placenta was not delivered within 30 minutes (Magann *et al*., 2005). Despite this current guidelines state the definition of prolonged third stage is made when the placenta has failed to be delivered 30 minutes after birth with active management of the third stage and an hour after expectant management (NICE, 2014). The degree of blood loss associated with a retained placenta is dependent on the type of placental retention: either trapped- separated from the uterine wall but not expelled due to cervical entrapment; adherens -caused by failure of myometrial contraction behind the placenta; or, a partial accreta where most of the placenta has separated, but a small piece is abnormally attached to the uterine wall (Weeks, 2008).

The longest delays in the current study were over 4 hours and associated estimated blood losses of 1300 ml and 1500 ml. When initial bleeding settled both cases were conservatively managed but both required prompt subsequent manual removal as bleeding increased. Whilst expectant management may be considered preferable for the women, without definitive diagnosis of cause of placental delay, it could be suggested failure to promptly deliver the placenta would constitute substandard care.

9.7.4 Hysterectomy

As previously described the rate of peripartum hysterectomy in the current study was comparable with the UK report using UKOSS (0.50 versus 0.55 per 1000 births). There remains wide variability in peripartum hysterectomy rates between and within countries. The impact of delay in attendance is highlighted in reported rates of 10.52 per 1000 deliveries in a tertiary centre in Pakistan. This is particularly stark when compared to the UK and Canada (0.80 per 1000 deliveries) (Knight, 2010; Glaze *et al*., 2008). In Turkey two recent reports demonstrate local differences in tertiary referral centre rates: 1.87 per 1000 deliveries (Kara, 2012) and 0.63 per 1000 deliveries (Karayalcin *et al.,* 2011). Karayalcin and colleagues, further identify the rate associated with CS as 2.0 per 1000 deliveries compared with 0.12 per 1000 deliveries following vaginal birth. All authors concede an association with both previous and current CS in increased risk of peripartum hysterectomy.

Peripartum hysterectomy is indisputably a major cause of maternal morbidity. One recent report suggested numbers are declining, identifying fewer cases of uterine rupture, but more cases of placenta accrete and percreta (Flood *et al*.,

2009). In the UK, a nationwide survey reported an estimated incidence of placenta accreta, percreta or increta of 1.7 per 10,000 maternities (95%CI 1.4 to 2.0) (Fitzpatrick *et al*., 2013). Half the cases were identified antenatally, and this was associated with lower blood loss at birth (1750 versus 3700 ml). Given recent advances in ultrasound and magnetic resonance imaging (MRI) further work regarding abnormal placentation could lead to more cases being identified leading to better informed women and well prepared staff, ultimately potentially improving outcomes for women. The management was variable, with Syntocinon infusion being the only universal therapy (Fitzpatrick *et al*., 2013).

9.8 Limitations

Adoption of documented blood loss from clinical records, with no attempt to verify blood loss by more robust methods such as gravimetric, biochemical, drapes or other method could be considered a major limitation of the current study. However the aim of this work was to ascertain current practice, and risk factors, therefore confirmation of documented blood loss was out with the remit of the current study. Some of the data imported and reviewed identified women who had both measured and visually assessed volumes of blood loss. Where these were both provided, the total blood loss was used for analyses. Despite the presence of calibrated drapes in both Centres, they were rarely used. When blood loss volume was documented as "measured", as opposed to "estimated", the method of measurement was seldom recorded. Thus in an ideal world more accurate means of assessing blood loss would be used, but the minimal use of calibrated drapes, suggests that, pragmatically, midwives and doctors rely on visual assessment. The aim of the STOP programme of work was to improve practice using routinely collected data and establish an audit cycle. Despite limitations of routinely collected data, the NHS Safety Thermometer for Maternity

is currently piloting blood loss as estimated from patient notes as an improvement indicator (www.safetythermometer.nhs.uk).

9.8.1. Study population

The demographics of the cohort could be considered as somewhat different from the general UK population. The inclusion of a tertiary referral and district general hospital increased generalisability in terms of social and ethnic diversity, but generalisability may be limited by not including a more rural population, or one less influenced by the proximity of London. Similarly the larger proportion of women living in areas of high deprivation (39% lowest quintile), and aged >30 years in the current cohort compared to contemporaneous maternity data for England and Wales (60% *versus* 47%) (ONS, 2010) may reduce generalisability. Although obesity rates were similar to recent national figures (15.2% *versus* 15.6%) (Heslehurst *et al.,* 2010). Comparison with UK maternal ethnic distribution at the time of the study (ONS, 2011) was not feasible as these data are not in the public domain (HESonline, 2009). Additionally error rates between electronic and handheld data could not be assessed for ethnicity due to the diversity of information collected in each participating unit. This must be addressed if the influence of ethnicity is to be considered in health and social analyses.

Historical comparison could have been influenced by the different methodology employed (case control versus weighted sample), changes in local service provision (one trust previously operating on two sites has now amalgamated maternity services to a single site, and the other is a new building in a new location), and shifting population demographics and profiles. Despite controlling

for known confounding variables, associations cannot necessarily be assumed to be causal. Gynaecological history, migration history, intended place of birth and degree of perineal trauma were not included.

9.8.2 Missing data

There was evidence of missing data related to blood loss, but this was resolved by our methodology. Overall, 7% (132/1896) of women had no recorded on NHS electronic summary data despite blood loss volumes being documented in their handheld notes. Of these, 27% (35 women) had a PPH ≥500 ml, 4% (5 women) of whom bled ≥1500 ml. Inherent problems with summary data have long been noted (Cleary *et al.,* 1994; Cartwright *et al.,* 1987). Fully electronic patient records have been advocated as improving care (Tindale and Hardiker, 2012; Feied *et al.,* 2004; Hammond *et al.,* 2003) and would facilitate monitoring of severe maternal morbidity if data quality was improved and consistent (Bouvier-Colle *et al.,* 2012; Chantry *et al.,* 2011). The completeness of written blood loss suggests that duplication of maternity records to electronic summary data, may be problematic in the participating units and further training may be required. Moving to a single entry electronic patient record system with automatic generation of summary data could improve discharge communication, ultimately improving postnatal care, but requires significant financial, development and training resource before such a system could be comprehensively introduced.

Thirty five women were identified via blood transfusion records. Of these: nine had documented estimated blood loss <500 ml; 18 had documented estimated blood loss 500-999 ml; two had documented estimated blood loss 1000-1499 ml; six had documented estimated blood loss exceeding 1500 ml. Transfusion protocols and documented symptoms, suggest estimated blood loss

underestimation in all cases which may in part be due to incorrect or absent addition of blood loss volumes documented.

In a few women, there was no information at all about blood loss, but these tended to be unattended or paramedic attended births. Paramedic and first aid training may require revision to include blood loss assessment after birth. Midwives arriving post-birth should also be reminded to comment on blood loss in addition to focusing on neonatal wellbeing.

Blood loss assessment following water birth was problematic, albeit a small proportion of the study population (1.07%). Centre 2, estimated categorically, <500 ml or >500 ml, Centre 1 recorded volume as for any other birth. It was unclear how this blood volume estimation was achieved, an issue that has been identified by others (Otigbah *et al.,* 2000). The RCOG/RCM state only healthy women with uncomplicated pregnancies should consider water birth (Al Zirqi *et al.,* 2006), this infers low risk of PPH but fails to address its' unpredictability. No recommendations exist regarding estimation of blood loss assessment (Munro *et al.,* 2008) with some suggesting visual assessment does not differ in water (Lim, 1994).

The largest source of missing data point was unfortunately 'temperature in labour' (27% of weighted sample), which proved significant in the final analyses. It would have been useful to have a complete data set although the association was so strong the lack data was not problematic. Maternal temperature above 37°C was associated with PPH and therefore omission may mean clinicians are unnecessarily unprepared.

9.9 Implications for policy and practice

As a result of this work there are several important implications for policy and practice:

1. The methodology employed in this study should be recommended as tool for monitoring PPH at all levels and could include cross check fields with other electronic summary data, such as ITU admission, transfusion and hysterectomy, which could ultimately improve care for women experiencing this common obstetric complication. The use of electronic patient records for monitoring and other outcomes is a valuable tool for research and clinical audit and the error rates in this study (up to 2% changed following comparison with other forms of medical records) provide an indication of how EPR systems can be used in the future. In a Trust a weighted sampling strategy could be devised to minimise the volume of review work whilst providing adequate power for confidence in findings. It should also be possible to expand the database to monitor other morbidities, such as shoulder dystocia, eclampsia, stillbirth, and aspects of care. The implementation of the minimal maternity dataset (HSCIC, 2013) should facilitate this process, unifying definitions and terminology. Ultimately this monitoring system could improve patient care, being a useful adjunct to the Confidential Enquiry in to Maternal Deaths and CNST audits.
2. The identification of errors in recording estimated, most commonly exaggerated by incorrect calculation or failure to update electronic patient records could be addressed by modifying handheld maternity records to include a pre-printed column on each postpartum page to document cumulative blood loss. Electronic discharge summary reports should include a requirement to input subsequent blood loss.

3. Blood loss assessment following water births also needs improvement. More accurate assessment and recording and addition of total blood loss, will improve patient care, enhance clinician confidence and provide better data for future audit and research.
4. Dissemination of the risk factors identified in the pre-pregnancy, pregnancy acquired and intrapartum models will inform health care providers and women regarding an individual's risk of PPH. This should result in improved patient care. For example specific consideration should be given to older and obese pregnant women, pregnancies achieved with ARTs, antenatal attendance feeling "generally unwell", women who receive steroids for fetal lung maturation, maternal temperature in labour and time to genital tract repair.

9.9 Future work

This study has identified areas requiring further investigation and development, these include:

1. Further expansion of the Internet based data management system needs to be explored in order to facilitate the adoption of approach into clinical use, so that PPH and other morbidities can be monitored locally, regionally and nationally.
2. The usefulness of the weighted sampling strategy employed here should be assessed in relation to research other morbidities within health care.
3. Further work is required to ascertain more accurately the true rates of blood loss at different levels in other geographical areas. The clinical utlility of the models will need validation. An algorithm to assess haemorrhage according to pre-existing, pregnancy acquired and intrapartum factors could be developed to better predict at what volume of blood loss a woman is likely to be compromised. As part of this process,

the mechanisms for informing women and health care professionals regarding risk of PPH should be investigated. Health care professionals will require additional education, which will necessitate the development of a training programme.

4. The knowledge gained through the risk models will provide information to facilitate the development of targeted strategies to reduce PPH, and increased understanding of cumulative risk.
5. Further investigation is required regarding several of the identified risk factors, especially the impact of Black African ethnicity.
6. More work is required around blood loss assessment in water, and training packages need to be developed for paramedics and "first aiders" regarding estimating blood loss during birth. New innovations developed in war medicine may improve the ability to assess blood loss more accurately. For example, haemostatic patch gauze and other dressings that absorb specific blood volumes, but not other body fluids. A randomised controlled trial investigating the effectiveness of these, versus traditional absorbent sheets and visual assessment of blood loss could be useful in targeting other readily available resources appropriately. Blood transfusion regimens have also been developed to improve prognosis and reduce overall blood product requirement in severe trauma. Investigation of the transferability of these initiatives to postpartum haemorrhage may reduce morbidities and improve care with concomitant advantages for women, their families and the NHS.
7. Unification of terminology and definitions is required to improve communication and care. Investigation into the appropriateness of the term "haemorrhage" when applied to a volume not likely to cause compromise should be challenged. The validity of different volumes of estimated blood loss according to mode of birth and other factors, such as maternal BMI, should be explored.

9.10 Summary and Conclusions

This study contributes to the body of literature regarding PPH. The derivation of clear models identifying independent risk factors for various levels of estimated blood loss should assist in the future management of this increasingly common emergency. It identifies novel risk factors and provides convincing supportive data for previously known risk factors. The main messages arising from this research are: i) Clinical estimation of blood loss and reporting of PPH data requires improvement, and much can be learned from the methodology used in this thesis; ii) Different risk factors predict different levels of PPH and as a result the concept of 'progression' may be misleading and a paradigm shift may be required based on the models developed as a result of this study, and iii) Many early variables positively associated with increased estimated blood loss are mediated by later events, many are not modifiable, but explanations are required when communicating with women and health care professionals. Simple measures, such as monitoring maternal temperature in labour and expedient genital tract repair, could have a significant impact on PPH outcomes.

Appendices

Appendix 1: STOP study protocol

PROJECT

Surveillance & Treatment

Of Postpartum

haemorrhage

PROTOCOL

Principal Investigator: Susan Bewley, Consultant Obstetrician

Co-Investigators: Annette Briley, Consultant Midwife

Mark Waterstone, Consultant Obstetrician
Jane Sandall, Professor of Midwifery
Melissa Clarke, Lay Advisor

Study Office: Maternal and Fetal Research Unit
10th Floor, North Wing
St Thomas' Hospital
London SE1 7EH

Tel: 020 7188 3641 **Fax:** 020 7620 1227

Funded by a grant from:

GUY'S & St THOMAS' CHARITY

INDEX

1 RATIONAL

Can the prediction, prevention, identification and treatment of obstetric haemorrhage be improved?

2 BACKGROUND

Bleeding can occur at any time during pregnancy. Serious haemorrhages can be antepartum, but most occur after delivery. The definition of postpartum haemorrhage (PPH) is: *"the loss of 500mls or more of blood from the genital tract within 24 hours of the birth of a baby"* (WHO,1989,1990; WHO ICD 10 version 2007, O72.0;O 72.1). Chandraharan and Arulkumaran (2007) further enhance the definition by suggesting PPH is blood loss of 1000 mls following caesarean section, and massive PPH refers to the loss of 30-40% (generally 2000 ml) of the patient's blood volume, resulting in alteration of haemodynamic parameters, leading to moderate to severe shock.

Incidence: Many studies report an incidence if 5% (eg Magann et al, 2005), but an Australian study reported 12% of women experience PPH following vaginal delivery (Henry et al, 2005). Known risk factors for PPH include caesarean section (elective, increases risk 4 fold, and emergency 9 fold), maternal age and obesity (2 fold increase in the risk). As all these factors are increasing, it is likely therefore that more women will experience PPH in the future.

Worldwide, PPH is a major cause of maternal mortality and morbidity. Lack of consensus regarding management of this common complication further compounds the consequences (Potts et al, 2006). Globally, the ability to identify and treat PPH is key to the effectiveness of maternity care In a previous study in the Region, severe maternal morbidity occured in 12 per 1000 deliveries. Sixty six percent of cases were secondary to massive PPH (>1.5 L) (Waterstone et al, 2001) and PPH is noted to have a high morbidity-to-mortality ratio.

Substandard care contributes to maternal mortality and morbidity (Geller et al, 2004; Pattinson et al, 2003) - cited in 60-67% of cases (1997-9:2000-2), with 80% of maternal deaths attributed to PPH, increasing from 10 to 17 (DoH, 2000; DoH, 2004). Professional factors and communication failure account for a large proportion of substandard care (Rowe et al, 2001). There is scope for reducing morbidity severity by evidence-based intervention as has been demonstrated in shoulder dystocia (Croft et al, 2006). Interdisciplinary learning facilitates multidisciplinary working (DoH, 2004).

Evidence exists regarding the prevention and treatment of PPH, but no simple unified national guideline exists in England, unlike cardiopulmonary resuscitation (CPR), for example. The evidence base for current provision and quality of care is limited. Mandatory emergency training (which every Trust adheres to as part of the Clinical Negligence Scheme for Trusts, CNST) complies with local requirements, with no uniformity or collaboration regarding instruction (Rodgers, 2007). There is no consensus regarding guidelines and monitoring of PPH, so national practice remains variable, unreported, non-standardised and incomparable. Discrepancies between actual and estimated blood loss volumes are cited as contributors to morbidity (Hall, 2004), with practice differing in this assessment. Currently neither the Royal College of Obstetricans and Gynaecologists (RCOG) nor National Institute for Health and Clinical Excellence (NICE) have proposed guidelines for PPH management.

Confidential Enquiry into Maternal and Child Health (CEMACH) recommendations have repeatedly included the following: unit protocols, ‘skills drills’, blood bank responsiveness, experienced operators for placenta praevia and early senior involvement. CNST mandates that units have a protocol for haemorrhage and annual skills training. The rise in maternal deaths suggests that recommendations are not translated into practice, there are increasing risk factors for PPH, and potentially declining working practices in struggling services. PPH is an emergency managed by a

multidisciplinary team assembling anew. Effective teamwork to agreed standards and protocols is vital.

The Scottish Obstetric Guidelines and Audit Project (SOGAP) produced guidelines regarding the management of PPH in Scotland (1998; 2002). These appear to have been adopted throughout the country, with minimal local variation. The Scottish Confidential Audit of Severe Maternal Morbidity advocates ongoing audit (Penney et al, 2005). It currently collects PPH data across Scotland, reporting annually. However, contributing factors, such as location, case mix and ITU accessibility, are not adjusted for when comparing units. Even with these caveats, they have reported consistent reductions in substandard care. No such monitoring system exists elsewhere in the UK. The rate of massive PPH (>2.5l) has increased from 3.7/ 1000 (CI 3.4.-4.0) over the 2003-5 triennium to 5.0/1000 (CI 4.4-5.6) in 2006, but there appears to be an increase in well-managed cases (from 63% in 2004 to 79% in 2006) (Penney & Adamson 2007)

Guidelines improve care (Grilli and Lomas, 1994); effective implementation and active dissemination involves taking local circumstances into account (O'Brien et al, 2005). Evidence suggests there is a lag between dissemination and implementation of guidelines, dependent on clinician behaviour. A North American survey stated 98% of obstetricians were aware of guidelines, but only 60% changed practice (DoH, 2000). Non-adherence increases risks to patients and litigation and NHS costs (Ranson et al, 2003).

The impact of these emergencies on health professionals has not been assessed or evaluated. Staff express anxiety and increasing stress following such events. Risk management procedures repeatedly identify delays in recognition, underestimation of blood loss, poor communication, inadequate teamwork, lack of senior involvement and non-adherence to guidelines as contributing factors. Other obstetric emergencies, eg shoulder dystocia, have been investigated and after system-wide policies have been implemented, complications have been reduced and staff confidence increased (Crofts et al, 2006). There has been little formal evaluation regarding skills-drills training for

emergency situations, with some suggestion that other methods may be more effective (Black and Brocklehurst, 2003). Effective ways of changing behaviour are audit and feedback of findings (Acker, 1991; O'Brien et al, 2005). Passive approaches are ineffective, but may raise awareness and reinforce messages. Multifaceted interventions targeting different aspects of behaviour are most effective (DoH, 2000). Future work should include qualitative process evaluations combined with randomised controlled trials (RCTs) to clarify how specific attributes of workshops influence professional practice (Thompson et al, 2001). Interactive educational workshops produce "moderately large changes" (O'Brien et al, 2005).

Many maternity services are undergoing reconfiguration with challenges of recruitment, retention and training, whilst providing 24 hour cover. In the last decade maternity services have not been a high priority (excepting CNST). Current NHS policy to increase care in the community and midwife-led care means that maternity networks and care pathways must be developed and operate efficiently to ensure high standards of care and safety.

NICE and RCOG recommendations have been ratified for many medical situations. None are in place regarding the management of PPH. UK Obstetric Surveillance System (UKOSS) recently investigated obstetric hysterectomy but this is the "tip of the tip of the iceberg". This project aims to develop an effective audit tool for monitoring PPH in participating units. By collecting data regarding smaller PPHs all strategies will be examined and the most effective in preventing massive blood loss investigated.

3 AIMS and OBJECTIVES

To undertake a detailed review of the available literature regarding the prediction, prevention, recognition and management of peripartum haemorrhage.

To investigate current practice regarding the management of peripartum haemorrhage from unit protocol and guidelines.

Using qualitative methodology:

- Investigate the professional, personal and team factors that influence the management of haemorrhage.
- Ascertain and examine multidisciplinary staff attitudes to the management of this complication.
- Explore the experience of haemorrhage from the sufferer's perspective. This will include their views of the professionals' response to the emergency and the impact on them and their families.

To develop a simple, unified protocol for the management of haemorrhage in the participating units, St Thomas' Hospital (STH) and Queen Mary's Hospital Sidcup (QMS)

To establish an internet-based data collection system to continuously monitor all haemorrhage and the quality of care in analysis of cases of severe haemorrhage. This will facilitate effective monitoring and auditing in participating units.

Following analysis of the information gained from the qualitative aspect of this study develop and test a training package to improve management of haemorrhage that will evolve and respond to identified needs, integrating theory and practice at STH and QMS.

Dependant on the results above, investigate the potential impact of setting up a self help/support group for women who have experienced PPH

4 DETAILED LITERATURE REVIEW

Electronic databases and journals will be used to obtain all relevant data regarding the prediction, prevention, identification and treatment of PPH,

using general and specific search strategies, which will be exploded and focused.

Current policy and guidelines

Initially, the policies and practices at STH and QMS will be compared and contrasted to ascertain current practice in a teaching hospital and a DGH, thus increasing generaliseability of findings.

Other maternity units will be approached regarding the guidelines they use for the management of PPH to investigate current availability of evidence based guidelines.

Unified protocol development

From the evidence found in the literature and from individual unit protocols a unified evidence-based protocol will be devised.

5 DATA COLLECTION

Internet based data collection /monitoring system

An Internet database will be developed to record data regarding all blood loss and the diagnosis and management of all PPHs (≥ 500mls). This will be a secure Internet site accessed with personalised passwords. Minimal demographic details will be recorded, and no individual will be identifiable from the data saved.

Several levels of access will be available:

Public page data: information will be available regarding the project and also about PPH.

Single unit : an individual will be only able to enter and see data relating to one maternity unit.

Administrator: this level the user will be able to access information from all participating centres, and edit (i.e. for data cleaning purposes). A data tracking system will be in place to ensure a retrievable audit trail reporting when and by whom data was altered, and also what was changed.

View only: this level of access allows all data to be viewed but none to be edited or altered.

The Internet data management system will be developed with MedSciNet™ Sweden. It is a Windows type interface with an Information tree - this means that additional information will only be collected when certain boxes are ticked. For example pre-existing medical condition, if marked no, no further information is required, if marked yes, additional internet "page" appears to record the information.

The information collected will probably include:

Maternal details: Gravida/Parity, Date of Birth, Ethnicity, Height, Weight (BMI will be calculated by the programme).

Previous obstetric conditions and events (eg PPH, CS),

Pre-existing maternal medical conditions (eg hypertension, diabetes, lupus),

Medicines

Pregnancy details: gestation at delivery, antenatal complications (e.g. pre-eclampsia, placenta praevia, antepartum haemorrhage, obstetric cholestasis),

Labour details: Place of delivery, onset of labour, mode of induction/augmentation, duration of 1st and 2nd stage of labour, mode of delivery, perineal/ vaginal trauma, management of 3rd stage

Estimated blood loss (EBL): measured/estimated, at delivery and postnatally (and including large APH)

Management of PPH: these datapoints are currently being developed and may include such things as staff involved, timing of arrival of senior staff etc. Paper copies of the database will be available as Appendix 2 of this manual, once development is complete.

DATA PROTECTION

All data will be collected and used within the context of the Data Protection Act (1998). No details of any particular woman will be released to any other organisation. Participating centres are registered with the Data Protection Agency.

6 QUALITATIVE STUDY

Face to face interviews (n dependant on data saturation) will be conducted with women who have EBL ≥ 500mls, and multidisciplinary team members involved in labour and delivery. These will be undertaken by two of the research team, audio taped (with permission) and field notes taken. Some interviews will be conducted using women and staff from the same event. Initially criterion sampling will be employed for quality assurance (Patton, 1990). Purposive sampling will ensure diversity of experience and data saturation (Patton, 1990). Using this mixed sampling combination will enhance triangulation. Staff sampling will involve the "cousin position" of diagonal (as opposed to vertical) sampling that minimises inhibition in organisational hierarchies (Wengraf, 2001).

The interview will focus on women's views of the management of the situation, what went well/badly, issues around communication between the multidisciplinary team and the women/partner, and their views of professional competence & teamwork. There is great interest in how patients can contribute to patient safety and these interviews can inform this work (Pandey, 2007). Critical incident technique will be utilised in this aspect of the study

ELIGIBILITY

Staff: Willing and able to give informed consent
Multidisciplinary
All grades
Diverse length of service

Women: Willing and able to give informed consent
PPH ≥500mls (in most recent delivery)
PPH during study period

RECRUITMENT PROCESS

- Eligible women and staff will be verbally asked to consider helping with this study.
- Staff and eligible women will be asked to read an information sheet about the study (Appendix 1).
- The study research midwife will contact staff/women and any queries or comments will be addressed.
- If the potential participant verbally agrees to take part an appointment will be arranged, at a mutually convenient time and place, to undertake the interview.
    - This will be in an appropriate setting for the interviewee
    - Adequate time will be available for this interview to take place
- At that interview, the researcher will answer any further queries.
- Informed written consent will be obtained from participants (Consent Form: Appendix 2).
- The interview will be recorded (with consent) and field notes taken.

INTERVIEW

The interviewee will be welcomed and explanation given regarding the taping of the interview and field notes being taken.

Confidentiality will be maintained at all times.

- Lightly structured depth narrative interview design, focusing on the elicitation and provocation of story-telling, will be utilised.
- Open-ended questions will be asked to allow the informant maximum opportunity to express thoughts and feelings.
- Subsequent queries will be developed from the information imparted.
- Clarification of certain points will be ascertained, as required.

  Any issues raised will be dealt with after the interview or referred appropriately with the participants' consent.

DATA ANALYSIS

Qualitative data will be analysed to examine emergent themes using the NVIVO7 software package. These data will be used to inform guidelines and develop training tools.

Data entered into the database will be analysed using the STATA9.0 software package. These data will be used to develop an effective monitoring system taking into account confounding variables such as client mix, skill mix and location.

7 QUANTATIVE ANALYSIS

We will obtain routinely collected data about all blood loss in the women delivering in STH and QMS over a year. From this we will derive estimates of adjusted mean blood loss for different levels of obesity, parity, mode of delivery, age group and ethnicity. Additional factors such as placental location and previous PPH or caesarean will be investigated depending on the quality of data available. We will look at frequency distributions of blood loss and examine preferred values and digit preference/avoidance. We will examine blood loss by time of day, day of week and public holidays.

We will examine the notes of a weighted sample of (1) women with blood loss <500mls (estimated 1%), (2) women with a PPH $\geq$500mls but <1,500mls (estimated 10%) and (3) all women with a massive haemorrhage ($\geq$1,500mls), in order to ensure data quality and to estimate the effects of all known risk factors (estimated total 300 sets of notes). We will also examine other sources in the cases of major haemorrhage $\geq$1500mls, (for example, delivery register, theatre log, risk reporting, blood transfusion laboratory, ITU and pharmacy) to ensure full ascertainment of cases.

We intend to use multiple logistic regression analysis to develop prediction models as with Waterstone et al (2001) for mean blood loss and proportion of women with severe blood loss (various cut offs can be used). These figures can be used to compare expected versus observed blood loss between centres. In addition we will be able to present new evidence of the relative

importance of various known and suspected risk factors. These figures will form the basis for power calculations and sample size determination for a future RCT.

8 ETHICAL ISSUES

The South East Multicentre Research Ethics Committee (MREC) has approved the study; Site Specific Information will be supplied to the Local Research Ethics Committee (LREC) for each participating centre.

9 PROJECT FUNDING

This project is funded by a grant from Guy's & St Thomas' Charity (Registered Charity Number 251983).

10 NHS and CLINICAL INDEMNITY

NHS indemnity will apply to women and clinical staff in respect of any injury or loss due to negligence by clinical staff during the study. This conforms with Department of Health guidelines, which state the NHS Trust Hospitals continue to have a duty of care to patients participating in research.

11 POLICY FOR PUBLICATION & AUTHORSHIP

Papers will be written collaboratively according to expertise and abiding by the international guidance for authorship or that of the appropriate journal. All contributions will be acknowledged. The results will be presented, in confidence, to the collaborators before publication.

12 TIMESCALE

The literature review, and subsequent protocol development will take approximately 1 year. The data monitoring system development and testing will start by the end of the first year. The complex intervention, in terms of training tools, will be developed in year 2. It is anticipated that by the end of year 2 the unified protocol will have been tested and accepted within participating units and the data monitoring system will provide an effective auditing tool for practice relating to PPH.

13 STUDY MANAGEMENT

The Principal Investigator, Dr Susan Bewley will share the overall responsibility of the study with the Clinical Trials Manager, Annette Briley. The day to day running of the trial will be undertaken by the Trial Management Team, Mrs Annette Briley and the study specific Research Midwife. Mr Paul Seed will provide statistical support. Laima Judosvainer will assist with IT. Mr Mark Waterstone will provide expert advice regarding maternal morbidity and oversee the study at QMS. Professor Jane Sandall will provide expertise regarding the qualitative aspects of the study.

14 PROJECT ADVISORY COMMITTEE

The Project Advisory Committee will meet regularly throughout the study to advise and monitor the programme of work (See GANTT Appendix 3). It has representation from maternity service users, clinicians and managers with expertise in postpartum haemorrhage, evaluation of complex interventions or educational/ training packages.

Membership:

Charles Wolfe, Professor of Public Health Medicine King's College London (Chairman);

Sue Eardley, Strategy Manager for Children and Maternity, Healthcare Commission

Sarah Gregson, Consultant Midwife, Maidstone and Tunbridge Wells, NHS Trust

Laura Pettigrew, lay representative recommended by National Childbirth Trust and pscychologist with special interest in early parenting

Graham Tydeman, Consultant Obstetrician, Fife NHS, Kirkcaldy, Scotland

Rachel Tribe, Senior Lecturer, Maternal and Fetal Research Unit, King's College, London

The co-investigators will also be part of this committee

The terms of reference of the Project Advisory Committee are:

- To provide advice on the overall conduct of the project to the management team
- To advise the project team on the research outputs
- To provide advice on the engagement of key stakeholders and dissemination of findings

Specific tasks are:

- To approve the main project protocol.
- To monitor and supervise the progress of the progress of the project towards its interim and overall objectives.
- To review at regular intervals relevant information from other sources.
- To advise and resolve problems brought to by the management team.
- To advise on study reports and papers for publication.

15 REFERENCES

Acker DB A shoulder dystocia intervention form Obstetric Gynecology 78(1): 150-1.1991

Black RS, Brocklehurst P. A systematic review of training in acute obstetric emergencies. BJOG 2003; 110(9): 837-41

Chanrahan E and Arulkumaran S. Massive postpartum haemorrhage and management of coagulopathy, Obstetrics and Gynaecology and Reproductive Medicine. 2007; 17:4

Crofts F, Bartlett, C and Ellis D et al (2006) Training for Shoulder Dystocia: A Trial of Simulation Using Low-Fidelity and High-Fidelity Mannequins, Obstetrics and Gynaecology 108(6) 1477-1485

DoH. Dept for Education and Skills National Service Framework for children, young people and maternity services. London 2004

DoH. Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 1997-1999. London 2000: HMSO

DoH. Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 2000-2002. London 2004: HMSO

Geller SE, Rosenberg D, Cox SM et al. The continuum of maternal morbidity and mortality: factors associated with severity. AmJOG 2004;191:939-44

Grilli R, Lomas J. Evaluating the message: the relationship between compliance rate and the subject of practice guideline. Med Care 1994;32:202-13

Hall MH. Haemorrhage: In Confidential enquiry into Maternal and Child Health. Why mothers die 2000 to 2003: report on the confidential enquiries into maternal deaths in the UK RCOG Press London 2004

Henry A, Birch MR,Sullivan EA etal, Primary postpartum haemorrhage in an Australian tertiary hospital; a case control study; Aust NZ Obstet Gynaecol 2005; 45(3): 233-6

Magann EF, Evans S, Hutchinson M et al. Postpartum hemorrhage after vaginal birth:an analysis of risk factors. South Med J 2005; 98(4): 419-22

O'Brien TMA, Freemantle M, Oxman AD et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. The Cochrane Database of Systematic Reviews 2005;2

Pandey K. WHO Launches list of nine solutions to improve patients' safety 2007 BMJ; 334 (7601): 974

Pattinson RC, Buchmann E, Mantel G et al. Can enquiries into severe adverse maternal morbidity act as a surrogate for maternal death enquiries? BJOG 2003;110:89-93

Patton M. Qualitative Evaluation and Research Methods (2nd edn) 1990. Newbury Park, Sage

Penney G, Adamson L, Kernaghan D. Scottish Confidential Audit of Severe Maternal Morbidity, 2nd annual report 2004. SPCERH 2005;25

Penney G, Adamson L. Scottish Confidential Audit of Severe Maternal Morbidity. 4th Annual Report (2006). SPCERH 2007:14-25

Potts, M, Hemmerling A The worldwide burden of PPH: policy development where inaction is lethal. 2006; 94 Suppl 2: S1; 16-21

Ransom SB, Studdert DM, Dombrovski MP et al. Reduced Medicolegal Risk by Compliance with Obstetric Clinical Pathways: A Case-Control Study. Obstet Gynaecol 2003;101;751-5

Rodgers K. Skills drills training: the way forward RCM Midwives 10(5):218-9 May 2007

Rowe RE, Garcia J, Macfarlane AJ, Davidson LL. Does poor communication contribute to stillbirths and infant deaths? A review J Pub Health Med 2001;23:23-4

Royston E, Armstrong S. Preventing maternal deaths. Geneva: World Health Organisation, 1989

Scottish Obstetric Guidelines and Audit Project (SOGAP), The Management of Postpartum Haemorrhage SIGN guideline 6, March 2002

Thomson OM, Freemantle N, Oxman A et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. The Cochrane Database of Systematic Reviews 2001;1

Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity; case-control study. BMJ 2001;322:1089-93

Wengraf T. Qualitative Research Interviewing. 2001.Sage. London.

WHO. The prevention and management of postpartum haemorrhage. Report of a Technical Working Group. 1990 WHO/MCH/90.7

16 APPENDICES

1. **Patient Information Sheet (PIS) version 3 28/06/07**
2. **Consent form**
3. **GANTT Chart**
4. **Flow chart**

Appendix 2: Initial Ethics approval and substantial amendment approval. Research and Development approval for Centre 1 and Centre 2.

NHS

National Research Ethics Service

South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713097
Facsimile: 01622 885966

22 November 2007

[redacted]

Dear Dr Bewley

Full title of study:	**STOP Study; surveillence and treatment of postpartum haemorrhage (PPH)**
REC reference number:	**07/H1102/79**

The REC gave a favourable ethical opinion to this study on 13 August 2007.

Further notification(s) have been received from local site assessor(s) following site specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s). I attach an updated version of the site approval form, listing all sites with a favourable ethical opinion to conduct the research.

R&D approval

The Chief Investigator or sponsor should inform the local Principal Investigator at each site of the favourable opinion by sending a copy of this letter and the attached form. The research should not commence at any NHS site until approval from the R&D office for the relevant NHS care organisation has been confirmed.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

07/H1102/79	**Please quote this number on all correspondence**

Yours sincerely

Miss Nicki Watts
Committee Co-ordinator

Email: nicki.watts@nhs.net

Enclosure: *Site approval form*

Copy to: *Mr David Selling*

South East Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	07/H1102/79	**Issue number:**	0	**Date of issue:**	22 November 2007
Chief Investigator:	Dr Susan Bewley				
Full title of study:	STOP Study; surveillance and treatment of postpartum haemorrhage (PPH)				

This study was given a favourable ethical opinion by South East Research Ethics Committee on 13 August 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* [1]
Mr Mark Waterstone	Consultant Obstetrician	Queen Mary's Hospital, Sidcup	Bexley & Greenwich Research Ethics Committee	22/11/2007	

Approved by the Chair on behalf of the REC:

..... (Signature of ~~Chair~~/Co-ordinator)
(delete as applicable)

N. WATTS (Name)

[1] *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension or termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK

07/H1102/79:	Please quote this number on all correspondence

sincerely

Miss Nicki Watts
Committee Co-ordinator

E-mail: nicki.watts@rhs.net

Enclosures — List of names and professions of members who were present at the meeting and those who submitted written comments

Copy to:

NHS
National Research Ethics Service
South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Tel: 01622 718097
Fax: 01622 885906

19 September 2008

Dear Dr Bewley

Study title:	**STOP Study; surveillance and treatment of postpartum haemorrhage (PPH)**
REC reference:	**07/H1102/79**
Amendment number:	
Amendment date:	**09 September 2008**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 18 September 2008.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non CTIMPs)		09 September 2008

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

South East Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 18 September 2008

Name	*Profession*	*Capacity*
Professor John Eastwood	Consultant Renal Physician	Expert
Dr L. Alan Roben	GP	Expert
Mr Roy Sinclair	Pharmacist	Expert

Telephone

10 October 2007

Dear .

ID: RJ1 07/0196 **STOP Study; surveillance and treatment of postpartum haemorrhage (PPH)**

Thank you for submitting your research project to the R&D Department. The project has now been approved by the Trust to take place in **Women's Health**. The project has been registered on the Trust's research database and given the R&D number **RJ1 07/0196**.

Please quote the R&D registration number in any communications with the R&D Department regarding your project.

Conditions of Approval:

The principal investigator must notify R&D of the actual start and end date of the project.

Please be aware that R&D approval is conditional upon ALL staff involved in the project within the Trust holding Trust substantive or honorary contracts.

Trust approval for the research is subject to the research being undertaken in line with the Department of Health's Research Governance Framework, and Trust policies relating to Research Governance. The Research Governance Framework and details of you and your researchers responsibilities within this framework can be found on the Department of Health's website at:

www.dh.gov.uk/policyandguidance/researchanddevelopment/researchanddevelopmentaz/researchgovernance/fs/en

or on the Trust's intranet at http://www.8080/article.asp?typeid=1&articleID=2218.

Please ensure that you and your researchers are aware of your responsibilities under this Framework.

In line with the Research Governance Framework your project may be randomly selected for monitoring for compliance against the standards set out in the Framework. For information, the Trust's process for the monitoring of projects and the associated guidance is available from the Trust's intranet or on request from the R&D Department. You will be notified by the R&D Department if and when your project has been selected as part of the monitoring process. No action is needed until that time.

Many thanks for registering your research project.

Yours sincerely

Clara Oguoma-Richards MSc
Research & Development Coordinator

NHS

NHS Trust

Research & Development

Tel: 020 8302 2678

06 November 2008

Consultant Obstetrician & Gynaecologist
Obstetrics & Gynaecology Department

Dear

Re: Surveillance and Treatment of Postpartum Haemorrhage (STOP) Study

Following receipt of all the necessary documentation, I can confirm on behalf of the Trust that you have full approval to undertake the above study at NHS Trust.

We look forward to receiving a copy of the results and/or any publication in due course.

Yours sincerely

Dr William Barry
Research & Development Director

Cc Annette Briley, Consultant Midwife/Clinical Trial Manager.
, AMD, Women & Children Care Group

Appendix 3: Imported data variables, and outcome variables definitions of categories, variables and terms, outcomes, exposures, risk factors, potential confounders, effect modifiers and diagnostic criteria listed in alphabetical order.

Variable (and abbreviation)	**Definition used and data obtained**	**Rationale for inclusion**
Importation and general data variables		
Centre	The maternity services included in the study. Centre 1- tertiary referral centre; Centre 2 -district general hospital.	Identification of place of birth and management of PPH.
Date of Import (date received)	The date information was electronically transferred to study specific data management system.	To facilitate contemporaneous identification of cases, and ensure ongoing reliability of system.
Digit Avoidance	Numbers avoided, usually due to documentation of those volumes requiring action, leading to lower numbers selected.	To explore the potential of a phenomenon described in blood pressure monitoring (Shennan and Halligan, 1996).
Digit Preference	Numbers preferred and therefore volumes rounded up or down to accommodate this preference.	To explore the potential of a phenomenon described in blood pressure monitoring (Shennan and Halligan 1996).
Extraction comments	Free text box on registration page- enables researchers to add any additional comments that might be relevant, but are not captured within the data	Free text should be kept to a minimum, but occasionally relevant data is not captured elsewhere (ECRIN., 2007).

	points.	
Estimated blood loss (EBL). Imported and confirmed	An estimation of the total blood volume lost, usually achieved by visual assessment. Imported volume (in ml) and confirmed volume (in ml)	Commonly used method of assessment in UK (Bose *et al.*, 2006). Imported; refers to the volume recorded on the NHS electronic summary data. Confirmed; refers to the volume documented following review of clinical data available from multiple sources.
Intramuscularly (IM)	Route of administration of drug into the muscle.	
Intravenously Intravenous (IV)	Route of administration of drug (or route of administration of drug or fluid into a vein.	
Maternal hospital number	Unique identifying number for all NHS patients treated in a specific unit.	To aid identification and location of medical records for weighted sample.
Postcode	The unique post office code assigned to a group of residences in England.	From this a super output area code is derived facilitating assessment of deprivation.
Threshold avoidance	An identified threshold is avoided, therefore typically lower volumes are recorded. Thresholds in blood loss are typically 500ml, 1000ml, 1500ml, 2000ml and 2500ml.	Identification and description of blood loss reporting errors.
Group A. Pre-pregnancy, pre-existing		
Assisted conception for this pregnancy	Yes/no No details required	Unknown impact on PPH.

Blood Pressure (BP) at booking	The measurement of systolic and diastolic blood pressure at first antenatal appointment measured in millimetres of mercury (mmHg)	Known association with hypertensive disorders of pregnancy
Body Mass Index (BMI)	Body weight divided by height squared in kg/m^2.	Described as causative of and protective against PPH at different levels (Paglia *et al.*, 2012)..
Depression	Maternal history of depression, or current depression, if current, medications taken.	Linked to PPH, especially certain medications (Tata *et al.*, 2007).
Ethnicity	The racial/genetic background from which a person originates. Within this study ethnicity was defined pragmatically, as used in the NHS. Most commonly with women identifying themselves within an ethic group.	Certain ethnic groups have been identified as at increased risk of PPH (RCOG guidelines; Al- Zirqi *et al.*, 2008; Magann *et al.,* 2005).
Epilepsy	Maternal history of epilepsy yes/no, If yes medications for epilepsy, and changes made in early pregnancy.	Association with epilepsy and treatments with adverse pregnancy outcomes (Borthen and Gilhus, 2012).
Female genital mutilation (female circumcision)	All procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for non-medical reasons(www.who.int).	Most radical procedures have a known associated with PPH (Banks *et al.*, 2006).

Gestation at booking	The number of weeks and days since last menstrual period when a woman first attends for antenatal care.	Delayed attendance for care can be an indicator of social exclusion and poor outcome (Lewis, 2007).
Gravida (G)	The number of times a woman has been pregnant, including current pregnancy.	Primiparity and grand multiparity are implicated as risk factors for PPH.
Index of Multiple Deprivation (IMD)	The level of social deprivation was estimated by matching every woman's postcode to a small area (Local Super Output Area, LSOA) of some 2,000 people, and then to the 2010 Index of Multiple Deprivation (IMD) for that LSOA (McLenan *et al.,* 2011).	Association between levels of social deprivation and many health outcomes reported (Oakley *et al.*, 1994; Docherty *et al.,* 2012).
Maternal date of birth (DOB)*	The date of birth of the pregnant woman/mother, expressed as day/month(numerical)/year.	Age automatically calculated from DOB, reducing errors. Age changes DOB does not.
Maternal height	Maternal height measured in centimetres (cm) at first antenatal appointment.	Used to generate BMI, which ultimately is used for customised birthweight centiles.
Maternal weight*	Maternal weight measured in Kilogrammes (Kg) at first antenatal appointment.	Used to generate BMI, which ultimately is used for customised birthweight centiles.
Parity (P)	The number of children born after 24 weeks'	Grand multiparity has been associated with PPH as has

	gestation.	primiparity (Dreissen *et al*., 2011).
Planned pregnancy	Did the woman plan to be pregnant at this time. Response, yes or no.	Could be associated with delayed engagement with maternity services and poor maternal preparation for pregnancy.
Pre-existing medical conditions	Options: Systemic Lupus Erythematosus (SLE); uterine anomaly; depression (requiring treatment); hypertension; FGM; other If other, free text box for details.	Conditions or treatments known to be associated with PPH.
Previous Caesarean section (CS)	Documented or maternally reported previous birth by Caesarean section (either elective or emergency) answer-yes/no If yes, how many?	Impact of previous CS variably reported (Al-Zirqi., 2010, Homer *et al.,* 2010) Kramer et al, 2011).
Previous PPH	Documented or maternally reported history of blood loss ≥500ml following previous birth.	Identified risk factor in current pregnancy (Ford et al, 2007).
Smoking at antenatal booking appointment	Options: yes/no Note: Self reported number of cigarettes smoked per day is notoriously unreliable and therefore was not recorded (Baker P.N., 2009)(Baker et al, 2009).	Associated with abnormal placentation (Werler, 1997; Guirgis *et al.*, 1997).

Systemic Lupus Erythematosus	Maternal history of Lupus, yes/no, If yes, any medications for this?	Known association with autoimmune diseases and pregnancy complications (Yasmeen *et al.*, 2001).
Group B: Pregnancy acquired		
Anaemia- last recorded Hb in pregnancy	Recorded in g/ml Date of last blood test dd/mm/yyyy (variable levels reported as significant for risk of PPH, RCOG guidelines, NICE 2007)	To enable assessment of antenatal anaemia and calculate change in Hb between this and postnatal results
Antenatal Admissions	Gestation age (weeks and days) and reason for admission (free text).	Investigatation of links between antenatal complications and PPH
Antenatal Anaemia	Haemoglobin (Hb) <11g/l, <10.5g/l, <10g/l antenatally, according to definition	PPH linked with antenatal anaemia (RCOG guidelines; Pavord *et al.*, 2011).
Antenatal Day Unit (ADU)	Did the women attend the antenatal day unit? Yes/no If yes how many occasions and reasons for attendance	Maternity triage. Women attended for many reasons, some with identified risk factors (ie APH), and potentially novel predictors could be identified.
Antepartum Haemorrhage (APH)	Bleeding from the birth canal after the 24th week of pregnancy	Identified risk factor for PPH
Antepartum Haemorrhage requiring hospital admission	Date; gestation (weeks and days); duration (days); amount (options: spotting, light, like a period, heavy/clots, transfusion required); causes of APH (unknown, placenta praevia, placental	Investigatation of the association between APH and PPH.

	abruption, local genital tract, fetal bleeding, low lying placenta, other)	
Generally unwell	Symptoms of lethargy, aches/discomfort, loss of appetite, not feeling "quite right". But all investigations showed no deviation from the normal, no diagnosis was made or treatment given.	Common reason for self referral for additional antenatal care. Initially considered as potential reason given for those experiencing domestic violence (RCM, 2006).
External cephalic version, (ECV)	The manipulation of the fetus, through the maternal abdomen, to a cephalic presentation (RCOG green top 20a).	Abnormal presentation may indicate poor uterine contractility (Hannah *et al*., 2000).
Gestational hypertension, (GHT)	Blood pressure higher than 140/90 on 2 occasions at least 4hours apart, without the presence of protein in the urine and diagnosed after 20 weeks of gestation.	Variably reported association with PPH.
Intended method of infant feeding	From the maternal records, planned method of infant feeding: breast, bottle, undecided.	Ascertainment the antenatal intention of the woman regarding method of feeding her baby.
Medication in pregnancy	Drop down box, multiple entries possible. Options: oral iron; IM iron; low dose Aspirin; Methyldopa; Labetalol; Nifedipine; Clexane; Thyroxine; Insulin; Metformin; oral	To investigate any relationships between medication taken in pregnancy and PPH.

	steroids- maternal health; IM steroids- fetal ling maturation; AN blood transfusion; Antibiotics; salbutamol; B12 injections; Ventolin; Becotide; Piriton; Temazepam.	
Obstetric cholestasis	Pruritis and liver dysfunction caused by oestrogen, Options: yes/no If yes, date diagnosed dd/mm/yyyy Gestation automatically calculated.	Some association with excessive blood loss at delivery (Kenyon *et al*., 2002).
Other infection in pregnancy	Yes/no.	To investigate any association between infection in pregnancy and PPH.
Placenta praevia (PP) (Major, minor, anterior and posterior)	The placenta attached to the lower uterine wall extending to or covering the internal cervical cs. Minor- the placenta reaches the lower uterine segment and partially covers the os. Major- the placenta is completely within the lower uterine segment and the internal os is occluded. Anterior – the placenta is either minor or major and attached to the anterior uterine wall. Posterior- the placenta	Identified risk factor for PPH (Waterstone *et al*., 2001; Watanabe and Matsubara, 2010).

	is either major or minor and is attached to the posterior uterine wall. Placenta praevia yes/ no, If yes, diagnosis made on ultrasound scan (with location) or at delivery (with location).	
Pre-eclampsia (PET)	New onset hypertension after 20th week of pregnancy and significant documented proteinuria.	Pre-eclampsia can be associated with abnormal placentation.
Pre-eclampsia screen (PET Screen)	Suspicion of pre-eclampsia. Serial BP measurements, urinalysis, blood tests- full blood count (FBC), liver function(LFT) and renal function tests, +/- growth scan.	Common reason for referral to ADU. Data collected to ascertain association between suspected PET and PPH.
Urinary tract infection (UTI)	Diagnosed UTI documented in the notes.	Associated with interventions (Humphrey and Tucker, 2009).
Warning antepartum haemorrhage (Warning APH)	1) Recurrent (at least 3 episodes; 2) like a period or heavier; 3) placental	
Group C: Intrapartum, Labour acquired		
Actions indicating recognition of PPH	Did attending clinicians undertake any action that might indicate response to excessive blood loss, such as: rub up contraction; nipple stimulation; head down	All actions suggest concern regarding blood loss, even though PPH may not be documented. Management of PPH was also investigated within the STOP study but outwith this

	tilt; oxygen; insert urinary catheter; suturing commenced; second dose of uterotonic; ergometrine; misoprostal; haemobate/carboprost; tranaexamic acid; IV fluid-crystalloid IV fluid-colloid; blood transfusion- emergency O Rh negative; blood transfusion type specific not cross matched; blood transfusion- cross matched; fresh frozen plasma given; platelets given; crypopreciptate given; Fibrinogen given; central venous pressure line inserted; urometer; bimanual compression; balloon tampanade; uterine artery embolization; bilateral ligation of internal iliac arteries; iliac artery clamped; aortic artery compression; aortic artery clamped; haemostatic uterine suturing (i.e.,B-Lynch); manual removal of placenta; examination under anaesthetic; laparotomy; uterine teat repaired; drainage of	thesis. This data point was included at two time points. This enabled information to be collected about both PPH immediately following delivery, and also at a later time point within the first 24 hours following birth. Some women had data entered at each time point, where an initial bleed was arrested but there was subsequently further bleeding. Date and time of first action enabled assessment of promptness of reaction to emergency.

	vulval haematoma; hysterectomy; vascular team involved; haematology team involved; transfer to HDU/ITU. If any of these were entered, date and time of first action dd/mm/yyyy: hh:hh.	
Additional blood information	Blood taken and sent, yes/no; if yes date and time sent dd/mm/yyyy: hh:mm Did the patient receive a transfusion? Yes/no Emergency O Rh Neg blood, yes/no Cross matched blood given, yes/no If yes, total number of units given Type specific unmatched blood given. Yes/no In total how many units did the woman receive? Was blood warming equipment used? yes/no/not documented Number of units of other blood products given: Fresh Frozen Plasma; Cryoprecipitate; Platelets; Fibrinogen: Factor VII; Autologous transfusion (ml)	Confirmed the frequency of blood taken for cross match and investigated the use of blood and blood products in this cohort. Information regarding the use of emergency blood supplies and warming equipment was a surrogate indicator of urgency and concern. These data were interrogated when the management of PPH was investigated- out with this thesis.
Administration of Misoprostol®	Did the woman receive misoprostol,	Misoprostol® has been identified as useful for IOL

	Yes/no.	and treatment of PPH (Gulmezoglu *et al.,* 2001).
Administration of Dinoprostone	Yes/no. If yes, total dose (number of pessaries).	Investigation of association with PPH.
Administration of oxytocin (Syntocinon®)	Yes/no, If yes, reason: to induce labour; to augment 1st stage of labour; to augment 2nd stage of labour. Total duration of oxytocin (Syntocinon®) administration hh:mm.	Investigation of association between oxytocin administration and PPH.
Admission to NICU/SCBU	Was the baby admitted to the neonatal intensive care unit (NICU) or special care baby unit (SCBU)? Response yes or no.	Identification of infants requiring additional support. Potentially indicative maternal problems, i.e. infection or severe PET or reason for delayed recognition of PPH.
Apgar scores Routinely assessed at 1 and 5 minutes of extrauterine life	Assessment of early neonatal wellbeing. Assesses respiration (crying), pulse (heart rate), reflexes (response to stimuli) skin colour (body & extremities) and muscle tone. Score out of 10 (2 for each) assessed at 1 minute and 5 minutes after birth (Apgar V.A., 1953).	Indicates fetal compromise caused by intrapartum problems i.e. bleeding, infection, prematurity, but also linked to causes of PPH (Finster and Wood, 2005).
Augmentation of labour	Labour is expedited where progress is slow.	Associated with PPH (Williams *et al*., 1998).
Baby's sex	Options: female; male; indeterminate	Facilitated calculation of customised birth weight

		centiles (www.grow.ac.uk)
Birth outcome	The status of the infant following birth: options were alive, intraurauterine fetal death (IUFD), death at delivery or death shortly after birth.	Stillbirth associated with PPH (Magann *et al*., 2005).
Birthweight	Birthweight- the weight of the baby shortly after birth in grams (g). Maximum birthweight- largest infant. Total birth weight- additive weight of all fetuses	Macrosomia has been associated with PPH, as have multiple pregnancies (NICE 2007; Magann *et al*., 2005).
Blood loss (BL) Blood loss measured/ estimated/both	Blood loss total volume measured in millilitres (ml) Often visually assessed and therefore estimated (EBL). Measured when blood loss excessive, but often total blood loss is a combination of measured and estimated (both).	Measurement of blood loss, routinely assessed visually (Bose *et al*., 2006) but other methods are more reliable with inherent limitations (Schorn 2010).
Blood loss at birth; how was this ascertained?	Total blood loss in ml. Tick boxes for measured, estimated or both	Ascertainment of how blood loss at birth was assessed
Blood loss subsequently	Volume lost after completion of third stage of labour, but within the first 24 hours postnatally Tick boxes for measured, estimated or	Ascertainment of how subsequent blood loss was assessed

	both	
Blood loss reported on discharge letter	Volume reported to primary health care providers (GP, community midwives, health visitors)	Ascertainment of the accuracy of information provided to colleagues
Blood loss total	Total blood loss volume at birth and in the 24 hours following	Recorded/documented total blood volume loss in each reviewed case
Caesarean section (CS)	Surgical delivery of infant through the abdomen	Identified risk factor for PPH (Kramer *et al*., 2011)
Caesarean section performed by	Grade of Doctor undertaking procedure. Drop down options: Consultant, Registrar, ST	Adherence to local policies and national guidelines regarding senior staff present at emergencies (RCOG 2009)
Causes of PPH	If non-atonic, was the PPH caused by: vaginal tears; cervical tears; inverted uterus; amniotic fluid embolism; blood disorders; uterine tear; placenta praevia; adherent placenta; retained products of conception; intraperitoneal bleed at CS; brisk loss at CS; broad ligament tears at CS; extension of incision angles at CS; oozing at CS; placental abruption; ruptured uterus; sepsis; vulval haematoma; unknown	Atonic uterus is cited as causative of 70% of PPH, therefore we decided to obtain details of all other causes (Oyelese and Ananth, 2010)
Customised birthweight centile	Centile produced using the principles of the	Customised centiles have the advantage of calculating

	Gestation Related Optimal Weight (GROW) method of assessing appropriateness of birthweight. Takes into account maternal height, maternal weight, ethnicity, parity, gestation at birth (in days), sex of infant, birth weight (www.gestation.net)	the appropriateness of birth weight of a baby according to maternal characteristics and gestational factors, Being more accurate than population centiles (Gardosi *et al*., 2011).
Date and time of delivery of placenta	dd/mm/yyyy, 24 hour clock hh:mm	To assess time between birth of baby and placenta
Date and time of ruptured membranes	dd/mm/yyyy ; 24 hour clock hh:mm	To investigate the impact of duration of ruptured membranes on PPH
Date of Delivery	The date on which a baby is born, expressed as day/month (numerical)/year	To ensure birth occurred in study time frame and assess whether knowledge of the ongoing study influenced PPH identification, management etc.
Date of Discharge	The date the mother (and baby) is transferred home following the birth. Expressed as day/month (numerical)/year.	To ascertain impact of intrapartum and early puerperium factors on duration of hospital stay.
Date of last blood test	dd/mm/yyyy	To calculate the gestation of last blood test in pregnancy.
Day of birth	The day of the week the birth occurred, calculated by database from date information.	To examine the influence of day of birth on PPH.
Documentation of PPH	Yes/no.	To identify whether the

in notes	If yes, date and time dd/mm/yyyy 24h clock hh:mm	blood loss was identified as PPH.
Evidence of Chorioamnionitis	Yes/no Inflammation of the amnion and chorion caused by bacterial infection. Typically ascending infection from the vagina, is associated with prolonged labour and preterm birth.	Known association between sepsis and PPH (NICE, 2008; Malabarey *et al.*, 2011).
Elective Caesarean section (elective S)	Planned surgical delivery, timed to suit mother and/or staff. Category 4 according to RCOG guidelines (Wickham et al, 2010).	To investigate associated with PPH (Al-Zirqi *et al*., 2009).
Emergency Caesarean section (emergency CS)	Surgical delivery performed due to fetal and/or maternal compromise, which may be life threatening (Brennand JE, 2010)	To investigate associated with PPH (Al-Zirqi *et al*., 2009).
Full blood count (FBC)	Date and time of result dd/mm/yyyy; hh:mm Haemoglobin (Hb); Platelets; White Blood cell count (WBC). In cases where multiple investigations are undertaken additional forms can be generated.	Investigation of the physiological response to blood loss and replacement, in addition to the management of the emergency.
Gestation at delivery	The number of weeks and days of pregnancy at which the baby is born.	Pre and post term birth have been variably reported as associated with PPH (Ushma Kiran et al., 2005).
Indication for induction	Drop down options:	IOL variably reported as

of labour (IOL)	postmaturity; macrosomia, Pre-eclampsia/PIH; IUGR; Obstetric cholestasis; Poor obstetric history; Maternal request; SPD; Fetal abnormality- live borth; fetal abnormality- fetocide; stillbirth; Multiple pregnancy; HELLP/ELLP syndrome; Fetal distress; sickle cell crisis; reduced fetal movements; APH; maternal medical condition; Diabetes/Gestational diabetes; Polyhydramnios; Unstable Lie.	impacting PPH (Stock *et al*., 2012; Magann *et al*., 2005). Indication for IOL might elucidate association.
Induction of labour	Labour is medically initiated with prostaglandins, artificial rupture of membranes and/or intravenous oxytocin (syntocinon®).	Variable description of the effects of induction on PPH (Stock *et al*., 2012; Magann *et al*., 2005; Malbarey *et al.*, 2011)
Inpatient stay Antenatal hospital nights Postnatal hospital nights	Number of antenatal nights in hospital and number of postnatal nights in hospital.	Facilitate assessment of costs of care.
Interval to suturing of perineum	The time between birth of baby and completion of suturing (hh:mm).	To investigate the relationship between delay in suturing and blood loss.
Last recorded micturition	Options: urinary catheter in situ; prior to 2nd stage; following delivery of baby; other.	To assess the impact of a full bladder on uterine contractility.

Management of third stage of labour	Tick box: Physiological; Oxytocin (Syntocinon®) IM; oxytocin (Syntocinon®) IV; Ergometrine Maleate/Oxytocin (Syntometrine®) IM; oxytocin (Syntocinon®) infusion increased; oxytocin (Syntocinon®) 40/50iu in 500ml commenced.	To ascertain current practice regarding the management of the third stage.
Maternal age at delivery	The age in years of the mother on the day she gave birth to her child (automatically calculated from maternal date of birth and baby's date of birth).	PPH has been variably associated with maternal age (Cameron *et al*., 2006; Montan *et al.,* 2007).
Maternal death	Yes/no If yes, date and time dd/mm/yyyy; 24 hour clock hh:mm.	To identify any woman in the cohort who died (regardless of cause).
Medications taken in the last week of pregnancy	Name of medication, daily dose For example, oral iron 2 tabs daily.	To investigate any relationships between medications taken in the week preceding birth.
Method of infant feeding on discharge home	How is baby feeding: exclusively breastfed; partially breastfed (has had at least 1 formula feed or water); mixed (has had several formula feeds in addition to breast milk); formula feeding (never put to breast).	To compare intended with actual method of infant feeding, when discharged.

Mode of delivery	The method by which a baby is born. Drop down box. Options: Spontaneous vaginal birth; instrumental vaginal birth; elective Caesarean section; emergency Caesarean section.	Each mode reported as influencing PPH rates (Sheiner *et al.*, 2005).
Multiple pregnancy	More than one fetus in utero. Additional data points were provided for each baby for multiple births enabling more than one answer to be given.	Associated with increased risk of PPH (Sebire *et al*., 2001).
Onset of labour	Options: spontaneous; induced; augmented; no labour-prelabour elective Caesarean section; no labour- pre-labour emergency Caesarean section; failed induction of labour –Caesarean section; stimulated prelabour rupture of membranes.	Onset of labour may influence mode of delivery, uterine contractility and PPH (Schott & Anderson, 2006; Robson *et al*., 2001).
Pain Relief	Options: none; trans-electrical nerve stimulation; water; opiates; epidural analgesia; spinal anaesthesia; general anaesthetic (GA); GA following failed epidural/spinal.	May influence uterine contractility and hormone production in addition to maternal mobility.
Perineal trauma	The state of the	Genital tract trauma causes

sustained and repair required	maternal perineum following the birth. Options: intact, 1st degree tear- not sutured; 1st degree tear -sutured; 2nd degree tear -not sutured; 2nd degree tear –sutured; 3rd degree tear; 4th degree tear; cervical tear; episiotomy; not known.	excessive blood loss being cited as one of the "4 Ts" (tissue, tone, *trauma* and thrombin).
Perineum sutured by	Grade of health care professional repaired perineum, options: NA; Student Midwife; Midwife; Medical Student; Doctor Consultant; Doctor Registrar: Doctor ST, if Doctor ST, grade.	To explore any associations between experience of health professional and blood loss.
Physiological third stage (or expectant management)	Following delivery of the baby no uterotonic drug is given, no fundal guarding or controlled cord traction. The placenta and membranes are left to separate and are delivered by maternal effort.	Used in low risk women with spontaneous labour and birth. Incidence and components vary (Prendeville *et al*., 1988).
Place of birth	The venue of birth. Options; home from home (centre 1); midwifery-led unit (centre 2); hospital birth centre (obstetric led units in both	To determine local practices in interventions and management.

	centres); home; other.	
Postnatal blood result data	Details of 3rd day postnatal blood results: Hb; platelets, white cell count.	To calculate fall in Hb from antenatal result.
Preterm prelabour rupture of the membranes (PPROM)	Breaking of the amniotic sac before labour and before 37 completed weeks of gestation.	Can be associated with chorioamnionitis and therefore PPH.
Reason for Caesarean section (CS)	Drop down options: previous CS-elective; failure to progress; macrosomia; failed IOL; failed ECV; multiple pregnancy; pre-eclampsia; placenta praevia; APH; Poor obstetric history; onstetric cholestasis; multiple pregnancy; failed instrumental; abdominal cerclage; reduced fetal movements; Breech; Fetal abnormality, Placental abruption; maternal request/tocophobia; Unstable lie; Previous 3rd degree tear; Maternal medical condition; cord prolapse; suspected scar dehiscence; uterine rupture; cervical fibroid covering Os; brow presentation; NA (no CS); not documented.	PPH could be attributed to CS but underlying reasons necessitating CS could cause the PPH. These data were collected to explore any such associations.

Resuscitation	Did the baby require support to initiate and establish extra-uterine life? Yes/no.	Identification of women where the condition of the baby could delay 3rd stage interventions.
Retained placenta	Yes/no If yes, management, options: oxytocin (syntocinon®) infusion; manual removal of placenta; hyperectomy.	To assess the impact of retained placenta on PPH and the efficacy of conservative versus surgical management.
Rupture of membranes (ROM) Spontaneous (SROM) Artificial (ARM)	Breaking of the amniotic sac. May occur spontaneously before or during labour (SROM) or medical staff rupture the membranes to induce or augment labour, referred to as artificial rupture of the membranes (ARM).	Can occur spontaneously, but ARM achieves augmentation and induction of labour both associated with PPH (RCOG guidelines; RCM, 2012a).
Sex of infant	Boy, girl or indeterminate.	Used to calculate birth weight centile
Spontaneous vaginal delivery (SVD)	A normal vaginal birth, without the assistance of a vacuum extractor or forceps.	Reference range for all instrumental deliveries.
Staff involved	Tick box for all grades of staff involved: student midwife; staff midwife; labour ward co-ordinator; medical student; doctor SHO; doctor SSHO; doctor registrar; doctor senior registrar; obstetric consultant; anaesthetic registrar; anaesthetic consultant; on call	Ascertainment of staff involvement at all levels in the management of this common obstetric complication. Lack of senior staff presence has been associated with adverse outcomes (Lewis 2004).

	haematologist; blood transfusion service; porters; theatre staff.	
Syntocinon® (Oxytocin) administration in the first or second stage of labour (prior to baby's birth)	Were uterotonics to introduce or increase contractility in the first and/or second stage of labour? yes/no If yes, duration of syntocinon administration.	Oxytocin (Syntocinon®) in the first and second stage of labour, prior to the birth has been variably reported as influencing the effectiveness of uterotonics in the third stage (Grotegut *et al*., 2011, Stock *et al.,* 2012).
Temperature in labour	Maximum temperature in labour. Measured in degrees centigrade above 37, with normal temperatures coded as 0.	Associated with signs of infection & chorioamnionitis. Whilst T>37 is common, varying degrees above this level have been introduced as alert levels on MEOWS charts (CMACE, 2011)
Time of birth	The time of day birth occurs (24h clock), hh:mm.	To ascertain whether time of birth influences incidence of PPH.
Time suturing competed	The time at which any repair to the genital tract is finshed	

* Maternal age imported in black if 20-30 years; yellow if 31-35 years; pink 35-40 years; and red when aged more than 40 years. Maternal BMI (Kg/m^2) was calculated and imported from height and weight entered on registration page in blue if <20 Kg/m^2; black if 20-25 Kg/m^2; orange in 25-29.9 Kg/m^2 and red if $\geq$30 Kg/m^2. Colour coding these data provided immediate visual warning for these previously identified risk factors (Dennedy et al, 2012; Montan, 2007).

References

Abalos E. 2009. Active versus expectant management of the third stage of labour. *RHL commentary.* Geneva: WHO.

Abasiattai A.M., Umoiyoho A.J., Utuk N.M., Inyang-Etoh E.C., Auuquo O.P. 2013. Emergency peripartum hysterectomy in a tertiary referral hospital in southern Nigeria.

Abdel-Aleem H., Singata M., Abdel-Aleem M., Mshweshwe N., Willams X., Hofmeyr G.J. 2013. Uterine massage to reducepostpartum hemorrhage after vaginal delivery. *Int J Gynecol Obstet*, 111, 3206.

Abdel-Aleem H., Singata M., Abdel-Aleem M., Mshweshwe N., Williams X., and Hofmeyr G. J. 2010. Uterine massage to reduce postpartum hemorrhage after vaginal delivery. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics,* 111**,** 32-6.

Abdel-Aleem H., Hofmeyr G.J., Shokry M., and El-Sonoosy E. 2006. Uterine massage and postpartum blood loss. *Int J Gynecol Obstet*, 93 (3), 238-9.

Abrahams C., and Davey K. 2002. Linking HES maternity records with ONS birth records. *Health Statistics Quarterly,* 13, 22-30.

ACOG. 2006. ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists, number 76, October 2006. Postpartum hemorrhage. *Obstetrics & Gynecology,* 108**,** 1039-1047.

Ahluwalia J., and Marriott L. 2005. Critical incident reporting systems. *Seminars in Fetal and Neonatal Medicine*, 10, 31-7.

Aibar L., Aguilar M.T., Puertas A., and Valverde M. 2013. Bakri balloon for the management of poostpartum hemmorrhage. *Acta Obstet Gynecol Scand*, 92, 465-7.

Ajenifuja K.O., Adepiti C.A., and Ogunniyi S.O. 2010. Postpartum Haemmorhage in a teaching hospital in Nogeria: a 5 year experience. *African Health Sciences*, 10 (1), 71-4.

Al J.F. 2012. Grandmulitparity:a potential risk for adverse pregnancy outcomes. *The Journal of Reporductive Medicine.* 57 (1-2), 53-7.

Al Kadri H.M., Al Anazi B.K., and Tanim H.M. 2011. Visual estimation versus gravimetric measuement of postpartum blood loss: a prospective cohort study. *Arch of Gynecol Obstet,* 283 (6), 1207-13.

Al-Zirqi I., Vangen S., Forsen L. and Stray-Pedersen B. 2008. Prevalence and risk factors of severe obstetric haemorrhage. *BJOG: An International Journal of Obstetrics & Gynaecology,* 115**,** 1265-1272.

Al-Zirqi I., Vangen S., Forsen L., and Stray- Pedersen B., 2009. Effects of onset of labor and mode of delivery on severe postpartum hemorrhage. *AmJOG,* 201**,** 273.e1-9.

Al-Zirqi I, Stray-Pederson B., Forsen L., and Vangen S., 2010. Uterine rupture after previous caesarean section. *BJOG,* 117**,** 809-20.

Alberti K.G.M.M. 2000. Multicentre research Ethics Committees: Has the Cure been Worse than the Disease? *BMJ*, 320, 1157-8.

Alexander J. 1999. Confusing debriefing and defusing postnatally: the need for clarity of terms, purpose and value,. *Midwifery,* 14**,** 122-4.

Alexander J., Thomas P. W., and Sanghera J. 2002. Treatments for secondary postpartum haemorrhage. *Cochrane Database of Systematic Reviews*.

Alexander J.M., Sarode R., McIntire D.D., Burner J.D., Leveno K.J. 2009. Whole blood in the management of hypovolemia due to obstetric hemorrhage. *Obstetrics and Gynecology*, 113 (6), 1320-6.

Alexander S., Bouvier.-Colle M.-H., Breaer G., Brocklehurst P, Cararach V., Deneux C., MacFarlane A., Prendiville W., Winter C., Zhang W-H., on behalf of EUPHRATES. 2005. Use of transparent plastic collector bags for estimation of blood loss in the third stage of labour: a cluster randomised trial. *Protocol*. Euphrates -Protocol-C-RCT-11-2005-approved at Collaborators meeting.

American College of Nurse-Midwives (ACNM) 2004. Joint statement: management of the third stage of labour to prevent post-partum haemorrhage. *Journal of Midwifery and Women's Health,* 49**,** 76-77.

Ananth C.V., Savitz D. A. and Luther E.R. 1996. Maternal cigarette smoking as a risk factor for placental abruption, placenta praevia and uterine bleeding in pregnancy. *Am J Epidemiol,* 144**,** 881- 890.

Api M., Api O., and Yayla M. 2005. Fertility after B-Lynch suture and hypogastric artery ligation. Fertility and Sterility, 84, 509.

Arrowsmith S., Wray S., and Quenby S. 2011. Maternal obesity and labour complications following induction of labour in prolonged pregnancy. *BJOG,* 118, 578-88.

Arulkumaran S., Mavrides E., Penney G.C., on behalf of the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists. 2009. Prevention and Management of Postpartum haemorrhgae. *Green top Guideline 52.* RCOG.

Apgar V.A. 1953. A Proposal for a New Method of Evaluation of the Newborn Infant *Anesthesia Analgesia,* 32**,** 260-7.

Ashworth A., and Klein A.A. 2010.Cell salvage as part of a blood conservation strategy in anaesthesia. *Br J Anaesth,* 105 (4), 401-16.

Awan N., Bennett M.J., and Walters W. 2011. Emergency peripartum hysterectomy: a 10-year review at the Royal Hospital for Women, Sydney.

The Australian & New Zealand journal of obstetrics & gynaecology, 51**,** 210-5.

Axe, S. 2000. Labour debriefing is crucial for good psychological care. *Br J Mid,* 8**,** 626-31.

Ayers S., Joseph S., McKenzie- Mcharg K., Slade P., Wijma K. and McKenzie-Mcharg K. 2008. Post-traumatic stress disorder following childbirth: current issues and recommendations for future research. *J Psychosom Obstet Gynaecol,* 29**,** 240-50.

Aylin P., Alexandrescu R., Jen M.H., Mayer E.K., and Bottle A. 2013. Day of the week procedure and 30 day mortality for elective surgery: retrospective analysis of hospital episode statistics. *BMJ,* 346: f2424 DOI: 10.1136/bmj.f2424

Babinszki A., Kerenyi T., Torok O., Grazi V., Lapinski R.H., and Berkowitz R.L. 1999. Perinatal outcome in grand and great-grand multiparity: Effects of parity on obstetric risk factors. *Am j Obstet Gynecol,* 181 (3), 669-74.

Bai S.W., Lee H.J., Cho J.S., Park Y.W., Kim S.K., and Park K.H. 2003. Peripartum hysterectomy and associated risk factors. *Journal of Reproductive Medicine*, 48 930, 148-52.

Bailey C. and Steer P. J. 2007. Maternal temperature in labour. *Fetal and Maternal Medicine Review* 18**,** 67-83.

Bailham D., and Joseph S. 2003. Post-traumatic stress following childbirth: a review of the emerging literature and directions for research and practice. *Psychology, Health & Medicine,* 8.

Baird D.D., Dunson D.B., Hill M.C., Cousins D., and Schectman J.M. 2003. High cumulative incidence of uterine leimyoma in black and white women: ultrasound evidence. *AmJOG*, 188, 100-7.

Bais J.M.J., Eskes M., Pel M., Bonsel G.J., and Bleker O.P. 2004. Postpartum haemorrhage in nulliparous women: incidence and risk factors in low and high risk women. A Dutch population-based cohort study on standard (≥500 ml) and severe (≥1000 ml) postpartum haemorrhage. *Eur J Obstet Gynecol,* 115**,** 166-72.

Baker P.N., Wheeler. S. J., Saunders T.A., Thomas J.E., Hutchinson C.J., Clarke K., Berry J.L., Jones R.L., Seed P.T., and Poston L. 2009. A prospective study of micronutrient status in adolescent pregnancy. *Am J Clin Nutr,* 89**,** 1114-24.

Bakri Y.n., Amri A., and Abdul Jabbar F. 20010. Tamponade-balloon for obstetrical bleeding. *Int J Gynaecol Obstet*. 74, 139-41.

Bakri Y.N. 1992. Uterine tamonade-drain for hemorrhage secondary to placenta previa-accreta. *Int J Gynaecol Obstet*, 37, 302-3.

Balki M., Dhumne S., Kasodekar S., Seaward G., and Caralho J.C.A. 2008. Blood transfusion for postpartum hemorrhage: A tertiary care hospital review. *JOGC*, 30 (11), 1002-7.

Banks E., M. O., Farley T., Akande O., Bathija H., Ali M., on behlf of the WHO Study Group on Female Genital Mutilation and Obstetric Outcome. 2006. Female genital mutilation and obstetric outcome: WHO collaborative prospective study in six African countries. *Lancet,* 367**,** 1835-41.

Barron K. 2007. The electronic patient record:written evidence. *The Stationary Office.* London

Baskett T.F., and O'Connell C.M. 2005. Severe obstetric morbidity: a 15 year population-based study. *J Obstet Gynaecol,*25 (1), 7-9.

Baskett T.F. 2002. Acute uterine inversion: a review of 40 cases. *JOGC,* 24, 953-6.

Bateman B.T., Mhyre J.M., Callaghan W.M., Kiklina E.V. 2012. Peripartum hysterectomy in the United States: nationwide 14 year experience. *Am J Obstet Gynecol*, 206 (63), e1-8

Bateman B.T., Berman M.F., Riley L.E., and Leffert L.R. 2010. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesthesia & Analgesia,* 110 (5), 1368-73.

Bhattacharya S., Campbell D.M., Liston W.A. and Bhattacharya S. 2007. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health* 7.168

Beck C.T. 2004. Post-Traumatic Stress Disorder Due to Childbirth. *Nursing Research,* 53**,** 216-224.

Begley C.M. 1990. A comparison of 'active' and 'physiological' management of the third stage of labour. *Midwifery,* 6**,** 3-17.

Begley C. M. 1991. Postpartum haemorrhage -who is at risk? *Midwives Chronicle,* 104**,** 102-106.

Begley C.M., Gyte G.M.L., Devane D., McGuire W., and Weeks A. 2011. Active versus expectant management for women in the third stage of labour (Review). *Cochrane Database of Systematic Reviews*, Issue 11. Art. No.: CD007412. DOI: 10.1002/14651858.CD007412.pub3.

Berg C.J., Callaghan Wm., Syverson C., and Henderson Z. 2010. Pregnancy-related Mortality in the United States, 1998-2005. *Obstet Gynecol,* 116, 1302-9.

Bewley S., Fawdry R., Cummings G. and Perry H., 2010. Electronic Health Records: the naked truth. *BMJ,* 341.

Bewley S., and Creighton S. 1997. 'Near-miss' Obstetric Enquiry. *J Obstet Gynaecol,* 17, 26-9.

Bhattacharya S., Campbell D.M., Liston W.A. and Bhattacharya S. 2007. Effect of Body Mass Index on pregnancy outcomes in nulliparous women delivering singleton babies. *BMC Public Health,* 7.

Bhella S., Gerard L., Lin Y., Rizoli S., and Callum J. 2012. Obstetric and trauma database review at a single institution firnds the optimal maternal age

restriction for the transfusion of O-blood to women incolved in traua to e 45 years. *Transfusion* 52, 2488-9.

Biaggi A., Paradisi G., De Carolis S., Lucchese A., and Caruso A. 2004. Maternal mortality in Italy, 1980-1996. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 114, 144-9.

Bibi S., Danish N., Fawad A. and Jamil M. 2007. An audit of primary post partum hemorrhage. *Journal of Ayub Medical College, Abbottabad : JAMC,* 19**,** 102-6.

Biguzzi E., Franchi F., Ambrogi F., Ibrahim B., Bucciarelli P., Acaia B., Radaelli T., Biganzoli E., and Mannucci P.M. 2012. Risk factors for postpartum hemorrhage in acohort of 6011 Italian women. *Thrombosis Research,* 129(4), e1-7.

Bingham D. 2012. Applying the generic errors Modeling System to Obstetric Hemorrhage Quality Improvement Efforts, *JOGNN* 41, 540-50.

Birthchoice U.K. 2010. *Highest and Lowest Home Birth Rates by Local Adminisrative Area* [Online] www.birthchoiceuk.com. [Accessed 06/02/2013 2013].

Birthplace in England Collaborative Group. 2011. Perinatal and maternal outcomes by planned place of birth for healthy women with low risk pregnanices: the Birthplace in England national prospectove cohort study. *BMJ,* 343.

Black R.S., and Brocklehurst P. 2003. A systematic review of training in acute obstetric emergencies. *BJOG: An International Journal of Obstetrics & Gynaecology,* 110**,** 837- 41.

Blalock H.M. 1972. *Social statistics* 2nd Edition. London McGraw-Hill.

Blomberg M. 2011. Maternal obesity and risk of postpartum hemorrhage. *Obstet Gynecol,* 118 (3), 561-8.

Bland M. 2000. *An introduction to Medical Statistics*. Chapter 8. 3rd Edition. Oxford, UK. Oxford University Press.

B-Lynch C., Croker A., Lawal A.H., Abu J., and Cowen M.L. 1997. The B-Lynch surgical technique for the control of massive postpartum haemorrhage: An alternative to hysterectomy? Five cases reported. *BJOG* 104, 372-5.

BMJ. 1964. Human experimentation: code of ethics of the World Medical Association. *BMJ*, 2, 117.

BMJ. 1962. Experimental medicine. *BMJ*, Oct 27, 1108-1109.

Bodelon C., Bernabe-Ortiz A., Schiff M.A., and Reed S.D. 2009. Factors associated with peripartum hysterectomy. *Obstet Gynecol*, 114 (1); 115-23.

Bodnar L.M., Siega-Riz A.M., Arab L., Chantala K., McDonald T. 2004. Predictors of pregnancy and postpartum haemoglobin concentrations in low-income women. *Publlic Health Nutr.*7 (6), 710-11.

Bodner K., Bodner-Adler B., Wierrani F., Mayerhofer K., Fousek C., Niedermayr A. and Grunberger W. 2002. Effects of water birth on maternal and neonatal outcomes. *Wiener klinische Wochenschrift,* 114**,** 391-5.

Bollapragada S.S., Norrie J.D. and Norman J.E. 2007. Review of new regulations for the conduct of clinical trials of investigational medicinal products. *BJOG*, 114, 917-21.

Bonnar J. 2000. Massive obstetric haemorrhage. *Best Practice and Research Clinical Obstetrics and Gynaecology,* 14**,** 1-18.

Bonnet M.P., Basso O., Bouvier-Colle M-H., Dupont C., Rudigoz R.C., Fuhrer R., and Deneux-Tharaux C. 2013. Postpartum Haemorrhage in Canada and France: A population-based comparison. *PLoS One,* 8 (6), e66882.

Bonnet M.P., Deneux-Tharaux C., Dupont C., Rudigoz R.C., Bouvier-Colle M.H. 2012. Transfusion practices in postpartum hemorrhage: a population-based study. *Acta Obstet Gynecol Scand*, 92, 404-13.

Bonnet M.P., Deneaux-Tharaux C., and Bouvier-Colle M.H. 2011. Critical care and transfusion management in maternal deaths from postpartum haemorrhage. *Euro JOG*, 158,2,183-8.

Bose P., Regan F. and Paterson-Brown S. 2006. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. *BJOG: An International Journal of Obstetrics & Gynaecology,* 113**,** 919-924.

Bouvier-Colle M-H., Mohangoo A.D., Gissler M., Novak-Antolic Z., Vutuc C., Szamotulska K., and Zeitlin J. 2012. What about the mothers? An anlysis of maternal mortality and morbidity in perinatal surveillance systems in Europe. *BJOG,* 119, 980-90.

Bouvier-Colle M-H., Ould El Joud D., Varnoux N., Goffinet F., Alexander S., Bayoumeu F., Beaumont E., Fernandez H., Lansac J., Levy G., and Palot M. 2001. Evaluation of the quality of care for severe obstetrical haemorrhage in three French regions. *BJOG,* 108**,** 898-903.

Bowling A. 2009. The principles of research. Chapter 6, p147. In: *Research Methods in Health*, 3rd edition, Open University Press, Maidenhead, England

Boyle D.I.R., and Cunningham S.G. 2002. Resolving fundamental quality issues in linked datasets for clinical care. *HMIC Mealth Management Information Consortium,* 8 (2), 73-7.

Boyle J.P., Honeycutt A.A., Venkat Narayan K.M.,Hoerger T.J., Geiss L.S., Chien H., Thompson T.J. 2001. Projection of Diabetes Burden Through 2050, impact of changing dempgraphy and disease prevalence in the U.S. *Diabetes Care,* 24 (11), 1936-40.

Brace V., Penney G., Hall M. 2004. Quantifying severe maternal morbidity: a Scottish population study. *BJOG: An International Journal of Obstetrics & Gynaecology,* 111**,** 481-4.

Brace V., Kernaghan D., Penney G. 2007. Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003–05. *BJOG: An International Journal of Obstetrics & Gynaecology,* 114**,** 1388- 96.

Brannen J. 1992. *Combining qualitative and quantitative approaches: an overview.,* Aldershot, Ashgate.

Breheny S., Healy D. L., Halliday J., Jaques A., Rushford D., Garrett C., Talbot J. M. and Baker G. H. W. 2009. Obstetric Haemorrhage after ART: An Analysis of 6730 Singleton Births. *Australian & New Zealand Journal of Obstetrics & Gynaecology,* 49 Sup**,** A3-A4.

Brennand J.E, Millins P., Yentis S., Hinshaw H.K.S on behalf of the Joint Standing Committee of the Royal College of Anaesthetists and Royal College of Obstetriciand and Gynaecologists. 2010. Classification of urgency of caesarean section-a continuum of risk. *Good Practice 11.* London: RCOG.

Brincat M., Versi E., Rodeck C.H. 1984. Full term precipitate labour. *Journal of Obsterics and Gynaecology,* 5**,** 96-7.

Bryant A., Mhyre J.M., Leffert L.R., Hoban R.A., Yakoob M.Y., and Bateman B.T. 2012. The association of maternal race and ethnicity and the risk of postpartum hemorrhage. *Anesthesia and Analgesia,* 115 (5), 1127-36.

Buckland S., and Homer C. S. E. 2007. Estimating bood loss after birth: Using simulated clinical examples. *Women and Birth: the Journal of the Australian College of Midwives,* 20**,** 85-88.

Bugg G.J., Stanley E., Baker P.N., Taggart M.J., and Johnston T.A., 2006. Outcomes of labours augmented with oxytocin. *Eur J Obstet Gynecol Reprod Biol,* 124**,** 37-71.

Buitendijk S., Gissler M., Macfarlane A., the PERISTAT scientific advisory committee 7. 2003. PERISTAT: Indicators from monitoring and evaluating perinatal health in Europe. *Eur J Public Health;* 13 (Suppl 1): 29-37

Burke G. and Duignan N.M. 1991. Massive obstetric haemorrhage. In *Progress in Obstetrics and Gynaecology,* Ed Studd J., volume 9, chapter 7, p 111-30. Edinburgh, Churchil Livingstone.

Cabacungan E.T., Ngui E.M., and McGinley E.L. 2012. Racial/ethnic disparities in maternal morbidities: a statewide study of labor and delivery hospitalizations in Wisconsin. *Maternal and Child Health Journal,* 16 (7), 1455-67.

Calder A.A., Loughney A. D., Weir C.J. and Barber J.W. 2008. Induction of labour in nulliparous and multiparous women: a UK, multicentre, open-label study of intravaginal misprostol in comparison with dinoprostone. *BJOG,* 115**,** 1279-88.

Callaghan W. M., Kuklina E. V. and Berg C. J. 2010. Trends in postpartum hemorrhage: United States, 1994-2006. *American Journal of Obstetrics & Gynecology,* 202**,** 353.e1-6.

Callaghan W.M., MacKay A.P., and Berg C.J. 2008. Identification of severe maternal morbidity during delivery hospitalisations, United States 1991-2003. *Am JOG*, 199, 133-8.

Calvert C., Thomas S.L., Ronsmans C., Wagner K.S., Adler A.J., and Fillippi V. 2012. Identifying Regional Variation in the Prevalence of Postpartum Haemorrhage: A systematic review and meta-analysis. *PLoS One,* 7 (7), e41114.

Cameron C. A., Roberts C. L., Bell J. and Fischer W. 2007. Getting an evidence-based post-partum haemorrhage policy into practice. *ANZJOG,* 47**,** 169-175.

Cameron C.A., Roberts C.L., Olive E.C., Ford J.B. and Fischer W.E. 2006. Trends in postpartum haemorrhage. *Australian & New Zealand Journal of Public Health,* 30**,** 151-156.

Cameron M.J. and Robson S. C. 2006. Chapter 3. Vital Statistics. *In:* B-Lynch C. (ed.) *Postpartum Haemorrhage.* Sapiens Medical.

Canfield M.A., Ramadhani T.A., Langlois P.H., and Waller D.K. 2006. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *Journal of Exposure Science & Environmental Epidemiology,* 16, 538-43.

Carolan M., and Hodnett E. 2007. With woman philosophy: examining the evidence, answering the questions. *Nursing Inquiry,* 14**,** 140-52.

Carroli G., Cuesta C., Abalos E., and Gulmezoglu A. M. 2008. Epidemiology of postpartum haemorrhage: a systematic review. *Best Practice and Research Clinical Obstetrics and Gynaecology,* 22**,** 999-1012.

Cartwright A., Jacoby A., and Martin C. 1987. Problems extracting data from hospital maternity records.*J Public Health,* 9 (3), 286.

Carvalho J.F., Cubal A., Torres S., Costa F., and do Carmo O. 2012. Emergency peripartum hysterectomy: a 10 year review. ISRN Emergency Medicine, Article ID 721918, 7 pages doi:10.5402/2012/721918, downloaded 23/04/2014.

Castaneda S., Karrison T., and Cibils L.A. 2000. Peripartum hysterectomy. *J. Perinat.Med*., 28, 472-81

Cawley J. and Burkhauser R.V. 2006. Beyond BMI:the value of more accurate measures of fatness and obesity in social science research. *NBER Working Paper Series,* 12291.

Centre for Maternal and Child Enquiries (CMACE). 2011. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006-08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdon. *BJOG*, 118 (suppl.1): 1-203

Chamberlain G. 2006. British maternal mortality in the 19th and early 20th centuries. *Journal of the Royal Society of Medicine,* 99**,** 559-63.

Chantry A.A., Deneux-Tharaux C., Cans C., Ego A.., Quantin C., Bouvier-Colle M-H., GRACE study group. 2011. Hospital discharge data can be used for

monitoring procedures and intensive care related to severe maternal morbidity. *J Clin Epidemiol,* 64 (9), 1014-22.

Chattopadhyay S.K., Kharif H. and Sherbeenu M.M. 1993. PLacenta praevia and accreta after previous caesarean section. *Eur J Obstet Gynecol Reprod Biol* 52: 151-6

Chapman V. 2004. Malpositions and malpresentations in labour*, In: The Midwives Labour ward Handbook.* Chichester, West Sussex, John Wiley & Sons.

Chattopadhyay S.K., Kharif H., and Sherbeeni M.M. 1993. Placenta praevia and accreta after previous caesarean section. *Eur J Obstet Gynecol Reprod Biol,* 52**,** 151-6.

Chediak J.R., Alban G.M., Maxey B. 1986. von Willebrand's disease and pregnancy: management during delivery and outcome of offspring. *AmJOG*, 155, 618-24.

Chen M., Zhang L., Wei Q., Xiaodong F., Gao Q., and Liu X. 2013. Peripartum hysterectomy between 2009 and 2010 in Sichuan, China. *Int J Gynecol Obstet*, 120, 183-6.

Chestnut D.H., Eden R.D., Gall S.A., and Parker R.T. 1985. Peripartum Hysterectomy: a Review od Cesarean and Postpartum Hysterectomy. *Obstet Gynecol*, 65 (3), 365-70.

Chhabra S., and Dhorey M. 2002. Retained placenta continues to be fatal but frequency can be reduced. *Journal of Obsterics and Gynaecology,* 22**,** 630-3.

Chibber R., Al-Hijji J., Fouda M., Al-Saleh E., Al-Adwani A.R., and Mohammed A.T. 2012. A 26-year review of emergency peripartim hysterectomy ina tertiary teaching hospital in Kuwait- Years 1983-2011. *Medical Principles and Practice*, 21, 217-22.

Chichakli L.O., Atrash H.K., Mackay A.P., Musani A.S., and Berg C.J. 1999. Pregnancy-related mortality in the United States due to hemorrhage: 1979-1992. *Obstet Gynecol*, 94 (5), 721-5.

Cho G.J., Kim L.Y., Hong H-R., Lee C.E., Hong S-C., Oh M-J.,and Kim H-J. 2013. Trends in the rates of Peripartum Hystetectomy and Uterine Artery Embolization. PLoSONE 8 (4), e60512, doi: 10.1371/journal.pone.0060512

Cho J.H., Jun H.S., and Lee C.N. 2000. Hemostatic suturing technique for uterine bleeding during caesarean section. *Obstetrics and Gynecology*, 96, 129-31.

Choi S-J., Song S.E.,Jung K-L., Oh S-Y., Kim J-H., and Roh C-R. 2008. Antepartum risk factors associated with peripartum cesarean hysterectomy in women with placenta praevia. Am J Perinat, 25 (1), 37-41.

Christopoulos P., Hassiakos D., Tsitoura A., Panoulis K., Papadias K., and Vitoratos N. 2011. Obstetric hysterectomy: A review of cases over 16 years. *JOG*, 31 (2), 139-41.

Chua S., Ho L. M., Vanaja K., Nordstrom L., Roy A.C., Arulkumaran S. 1998. Validation of a laboratory method of measuring postpartum blood loss. *Gynecol Obstet Invest,* 46**,** 31-3.

Cipriani A., and Gedded, J. 2003. Comparison of systematic and narrative reviews: the example of the atypical antipsychotics. *Epidemiologia e Psichiatria Sociale*. 23 (3), 147-53.

Clark S.L., Pjelan J.P., Yeh S.Y., Bruce S.R., Paul R.H. 1985. Hypogastric Artery Ligation for Obstetric Hemorrhage. *Obstet Gynecol*, 66 (3), 353-6.

Claudius I., Behar S., Ballow S., Wood R., Stevenson K., Blake N., Upperman J.S. 2008. Disaster drill exercise documentation and management: are we drilling to standard? *J Emergency Nursing,* 34**,** 504-8.

Cleary R., Beard R.W., Coles J., Roberts S., Schumacher D., and Wickings H.I. 1994. The quality of routinely collected maternity data. *BJOG,* 101 (12), 1042-7.

Cleary-Goldman J. and Robinson J.N.2003. The Role of Episiotomy in Current Obstetric Practice. *Semin Perinatal,* 27 (1), 3-12.

Clinical Negligence Scheme for Trusts. 2003. Clinical Risk Management Standards for Maternity Services. *Criterion 5.2.1*. https://www.gov.uk/government/publications/guidance-for-use-of-the-clinical-negligence-scheme-for-trusts-cnst

CMACE. 2011. Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08.

Coggan D. 2003. *Statistics in Clinical Practice,* London, BMJ Books.

Cohen L. 2012. Systematic underestination of blood loss. *Anaesthesia,* 67, 1178-9.

Combs C.A., Murphy E. L. and Laros R.K. JR. 1991. Factors associated with postpartum hemorrhage with vaginal birth. *Obstetrics and Gynecology,* 77**,** 69-76.

Combs C.A. and Lakros R. K. 1991. Prolonged Third Stage of Labor: Morbidity and Risk Factors. *Obstet Gynaecol,* 77**,** 863-7.

Conde-Agudelo A., Rosas-Bermudez A., Kafury- Goeta A.C. 2007. Effects of birth spacing on maternal health: a systematic review. *Am JOG*, 196 (4), 297-308.

Condous G.S., Arulkumarah S., Symonds I., Chapman R., Sinha A., Razvi K. 2003. The "tamponade test" in the management of postpartum hemorrhage. *Obstet Gynecol*, 101, 767-72.

Cook H., Ezzati M., Segars J. H., and McCarthy K. 2010. The impact of uterine leiomyomas on reproductive outcomes. *Minerva ginecologica,* 62**,** 225-36.

Cook R. 2008. Chorioamnionitis, maternal fever, and neonatal encephalopathy. *Development Medicine and Child neurology,* 50, 9.

Cosgrove S.A. 1936. Obstetric hemorrhage and its management *South Med J*, 29, 1219-25.)

Costello A., Osrin D., and Manandhar D. 2004. Reducing maternal and neonatal morbidity in the poorest countries. *BMJ,* 329 (7475), 1166-9.

Cotter A., Ness A., and Tolosa J. 2001. Prophylactic oxytocin for the third stage of labour. *Cochrane database Syst Rev,* 4, CD001808.

Coulter-Smith S.D., Holohan M. and Darling M.R.N. 1996. Previous caesarean section: a risk factor for major obstetric haemorrhage. *Journal of Obstetrics & Gynaecology,* 6**,** 349-52.

Cresswell J.W. 2009. *Research design: qualitative, quantitative and mxed methods approaches*, Sage Publications, London.

Cresswell J.W. 2002. *Research Design: qualitative, quantitative and mixed methods approaches*. Second Edition, Sage Publications, London.

Crofts J.F.D., Ellis D., Draycott T.J., Winter C., Hunt L.P., and Akande V.A. 2007. Change in knowledge of midwives and obstetricians following emergency training: a randomised trial of local hospital, simulation centre and teamwork training. *BJOG,* 114**,** 1534-41.

Cronin P., Ryan F., and Coughlin M. 2008. Undertaking a literature review: a step-by-step approach. *British Journal of Nursing*, 17 (1), 38-43.

Crozier T. M., and Wallace E. M. 2011. Obstetric admissions to an integrated general intensive care unit in a quaternary maternity facility. *Australian & New Zealand Journal of Obstetrics & Gynaecology,* 51**,** 233-238.

Czikk M.J., McCarthy F.P., and Murphy K.E. 2011. Chorioamnionitis: from pathogenesis to treatment. *Clinical Microbiology and Infection,* 17 (9), 1304-11.

Data Protection Act 1998. Section 33(2). www.uk-legislation.hmso.gov.uk/acts/acts1998/19980029.htm. Accessed 16/06/2014.

Davis D., Baddock S., Pairman S., Hunter M., Benn C., Anderson J., Dixon L., Herbison P., Berkeley C. 2012. Risk of severe postpartum hemorrhage in low-risk childbearig women in New Zealand: exploring the effect of place of birth and comparing third stage management of labor. *Birth*. 39 (2), 98-105.

Davis K. 2005. Leading the midwifery renaissance. *RCM annual conference, Harrogate, presentation.*

Davis-Floyd R. 2003. *Birth an American Rite of Passage*, University of California Press.

De Longe L., Bos H.J., van Langen I.M., de Jong-van den Berg L.T.W., and Bakker M.K. 2013. Antibiotics prescribed before, during and after pregnancy in the Netherlands:a drug utilization study. *Pharmacoepidemiology and Drug Safety.* ePub DOI 10.1002/pds.3492

De Loor J.A., and van Dam P.A. 1996. Foley catheters for uncontrollable obstetric or gynecologic hemorrhage, *Obstet Gynecol*, 88, 737-8.

De Montjoie A.J.2009. Introducing the CDISC Standards: New Efficiencies for Meical Research. *CDISC Publications*. www.cdisc.com Accessed 18/06/2014

Demirci O., Tugrul A.S., Yilmaz E., Tosun O., Demirci E and Eren Y.S. 2011. Emergency peripartum hysterectomy in a tertiary obstetric center: nine years evaluation. *J Obstet Gynaecol Res*, 37 (8), 1054-60.

Deneux-Tharaux C., Berg C., Bouvier-Colle MH., Gissler M., Harper M., Nannini A., Alexander S., Wildman K.,Breart G.and Buekens P. 2005. Underrporting of Pregnancy-Related Mortality in the United States and Europe. *Obstet Gynecol,* 106**,** 684-92.

Deneux-Tharaux C., MacFarlane A., Winter C., Zhang W., Alexander S. and Bouvier-Colle M. 2009. Policies for manual removal of placenta at vaginal delivery: variations in timing within Europe. *BJOG,* 116**,** 119-124.

Denison F.C., Price J., Graham C., Wild S., Liston W.A. 2008. Maternal obesity, length of gestation, risk of postdates pregnancy and spontaneous onset of labour. *BJOG,* 115 (6), 720-5.

Department of Health. 2006. *Best Research for Best Health: A new national health research strategy.* DOH Whitehall, London.

Department of Health. 2003.*Confidentiality: NHS Code of Conduct*, Version 3. London: DoH. www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf. Accessed 16/06/2014.

Department of Health and Human Services. 1997. "21 CFR Part 11, Electronic Records; Electronic Signatures Final Rule", *Federal Register* 62 (54), 13429.

Devine P. C. 2009. Obstetric hemorrhage. *Seminars in Perinatology,* 33**,** 76-81.

Devine P. C. and Wright, J. D. 2009. Obstetric hemorrhage. Introduction. *Seminars in Perinatology,* 33**,** 65-75.

Dewhurst C.J., Dutton W.A.W. 1957. Recurrent abnormalities of the third stage of labour. *Lancet*, 272, 764-7.

Dhanjal M.K. 2009. The older mother and medical disorders of pregnancy. Series Editors:Bewley S., Ledger W., Nickolou D., Kehoe S. *Reproductive Ageing,* London, RCOG Press.

Diabetes UK. 2012. Diabetes in the UK 2012: Key statistics on diabetes.

Diejomaoh M.F.E., Al-Shamali I.A., Al-Kandari F., Al-Qemae M., Mohd A.T. 2006. The reproductive performance of women at 40 years and over. *Eur J Obstet Reprod Biol,* 126, 33-8.

Dildy G.A 3RD., Paine A. R., George N.C. and Velasco C. 2004. Estimating blood loss: can teaching significantly improve visual estimation? *Obstet Gynaecol,* 104**,** 601-6.

Ding D-C., Hsu S., Chu T-W., Chu T-Y., 2006. Emergency peripartum hysterectomy in a teaching hospital in Eastern Taiwan. *J Obstet Gynecol*, 26 (7), 635-8.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approxiamtion of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practoce in the conduct of clinical trials on medicinal products ofr human use. *OJ*, 2001, L121, 34-44.

Dombrowski M.P., Bottoms S.F., Saleh A.A., Hurd W.W., and Romero R. 1995. Third stage of labor: analysis of duration and clinical practice. *AmJOG,* 172, 1279-84.

Doran J.R., O'Brien S.A., Randall J.H. 1955. Repeated postpartum hemorrhage, *Obstet Gynecol*, 5, 186-92.

Doumouchtsis S.K., Papageorghiou A.T., Arulkumaran S. Systematic review of conservative management of postpartum hemorrhage; what to do when medical treatment fails. *Obstet Gynecol Surv*, 62, 540-7.

Driessen M., Bouvier-Colle M-H., Dupont C., Khoshnood B., Rudigoz R.C., Deneux-Tharaux C., Pithagore6 Goup. 2011. Postpartum hemorrhage resulting form uterine atony after vaginal delivery: factors associated with severity. *Obstet Gynecol,* 117 (1), 21-31.

Drife J.O. 1997. Lessons to be mearnt from maternal mortality reports. *Current Obstetrics and Gynaecology*, 7, 218-23.

Drife J. 1993. Maternal "near miss" reports? *British Medical Journal,* 307**,** 1087-8.

Du Vigneaud V., Ressler C., Swan J.M., Roberts C.W., Katsoyannis P.G. and Gordon S. 1953. The synthesis of an octapeptide with the hormonal activity of oxytocin. *J Am Chem Soc,* 75**,** 4879-80.

Dupont C., Occelli P., Deneux-Tharaux C., Touzet S., Duclos A., Bouvier-Colle M-H., Rudigoz R-C., and Huissoud C. 2014. Severe postpartum haeorrhage after vaginal delivery: a statistical process control chart to report seven years of continuous quality improvement. *Eur J Obst Gyn Reprod Biol*. 178, 169-76

Duff C., and Sinclair M. 2000. Exploring the risks associated with induction of labour: a retrospective study using NIMATS database. *Journal of advanced nursing,* 31**,** 410-7.

Dunne F. 2005. Type 2 diabetes and pregnancy. *Seminars in Fetal and Neonatal Medicine,* 10**,** 333-9.

Dunne F., Brydon P., Smith K., and Gee H. 2003. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. *Diabetes Medicine,*30, 734-8.

Duthie S.J., Ven D., Yung G.L.K., Guang D.Z., Chan S.Y.W., and Ma H.K. 1990. Discrepancy between laboratory determination and visual estimation of blood loss during normal delivery. *Eur J Obstet Gynecol Reprod Biol*, 38, 119-24.

ECRIN. 2007. *Summary of criteria to ensure GCP compliance for data managment* [Online]. European Clinical Research Infrastructure Network (ECRIN). Available: http://www.ecrin.org [Accessed 20/12/2010].

Edouard L., and Senthilselvan A. 1997. Observer error and birthweight: digit preference in recording. *Public Health,* 111, 77-9.

Ehrenthal D.B., CHichester M.L., Cole O.S., Jiang X. 2012. Maternal Risk Factors for Peripartum Transfusion. *Journal of Women's Health* 21 (7), 792-7.

El Emam K., Jonker E., Sampson M., Krieza-Jeric K., and Neisa A. 2009. The Use of Electrnic Data Capture Tools in Clinical Trials: Web-Survey of 259 Canadian Trials. *Journal of Internet Medical Research* 11 (1) e8 www.jmir.org/2009 Accessed 18/06/2014.

El-Hamamy E., and B-Lynch C. 2005. A worldwide review of the uterine compression suture techniques as alternatives to hysterectomy in the management of severe post-partum haemorrhage. *J Obstet Gynaecol*, 25 (2), 143-9.

El-Jallad M.F., Zayad F., and Al-Rimawi H.S. 2004. Emergency peritpartum hysterectomy in Northern Jordan: indication and obstetric outcome (an 8 year review). *Arch Gybecol Obstet*, 270 (4), 271-3.

Engelsen I.B., Albrechtsen S., and Iversen O.E. 2001. Peripartum hysterectomy-incidence and maternal morbidity. *Acta Obstet Gynecol Scand*, 80 (5), 409-12.

Eriksson A.W. and Fellman J. 2007. Temporal trends in the rates of multiple maternities in England and Wales. *Twin research and human genetics : the official journal of the International Society for Twin Studies,* 10**,** 626- 32.

Erman Akar M., Saygili Yilmaz E., Yuksel B., Yilmaz Z. 2004. Emergency peripartum hysterectomy. *European J Obstet Gynecol*, 113, 178-81.

Eskild A., and Vatten L.J. 2009. Abnormal bleeding associated with preeclampsia: A population study of 315,085 pregnancies, *Acta Obstet Gynecol Scand,* 88, 154-8.

European Clinical Research Infrastructure Network (ECRIN). 2007. Summary of criteria to ensure GCP compliance for data management. www.ecrin.org Accessed 18/06/2014.

Euro-Peristat Project, with SCPE and EUROCAT. 2013. The health and care of pregnant women and babies in Europe 2010. www.europeristat.com Accessed 27/10/2013.

EUROPERISTAT project in collaboration with SCPE, EUROCAT and EURONEOSTAT. 2008. European Perinatal Health Report. Ed Zeitlin J. and Mahangoo M. Available: http://www.europeristat.com (Accessed 13/10/2013).

Falconer C. 2000. *House of Lords Hansard*. www.parliament.the-stationary-office.co.uk/pa/Id199900/ldhansard/vo001114-35.htm (accessed 16/06/2014)

Farrar D., Tuffnell D., Airey R. and Duley L. 2010. Care during the third stage of labour: a postal survey of UK midwives and obstetricians. *BMC Pregnancy and Childbirth,* 10**,** 23.

Fawcus S., and Moodley J. 2013. Postpartum haemorrhage associated with caesarean section and caesarean hysterectomy. *Best Practice & Research in Clinical Obstetrics & Gynaecology,* 27 (2), 233-49.

Fawdry R., Bewley S., Cumming G., and Perry H. 2011. Data re-entry overload: time for a paradigm shift in maternity IT? *J R Soc Med,* 104**,** 405-12.

Feied C.f., Handler J.A., Smith M.S., Gillam M., Kanhouwa M., Rothenhaus T., Conover K., and Shaanon T. 2004. Clinical Information Systems: Instant Ubiquitous Clinical Data for Error Reduction and Improved Clinical Outcomes. *Academic Emergency Medicine,* 11, 1162-9.

Fenger-Eriksen C., Lindberg-Larsen M., Christensen A.Q., Ingerslev J., and Sorensen B. 2008. Fibrinogen concentrate substitution therapy in patients with masssive haemorrhage and low plasma fibrinogen condentrations. *Br J Anaesth* 101, 769-73.

Field, A. 2009. Logistic Regression. *In:* Field A. (ed.) *Discovering Statisics Using SPSS. Third Edition.* London: Sage Publications.

Filmer P., Philipson M., Silverman D, and Walsh D. 1972. *New Directions in Sociological Theory*. London Collier-Macmillan.

Finster M., and Wood M. 2005. The Apgar Score Has Survived the Test of Time. *Anaesthesiology,* 102**,** 855-7.

Fitzpatrick K.E., Sellers S., Spark P., Kurinczuk J.J., Brocklehurst P., and Knight M. 2013. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based study. *BJOG*, 121, 62-71.

Fitzpatrick M., Harkin R., McQuillan K., O'Brien C., O'Connell P.R., and O'Herlihy C. 2002. A randomised clinical trial comparing effects of delayed versus immediate pushing with epidural analgesia on mode of delivery and faecal incontinence. *BJOG*, 109, 1359-65.

Fleming D., Gangopadhyay R., Koroshi M., and Arulkumaran S. 2012. Maternal Deaths from Major Obstetric Hemorrhage in the UK: Changing Evidence from the Confidential Enquiries. Eds Arulkumaran S., Karoshi M., Keith L.G., Lalonde A.B., B-Lynch C. A Comprehensive textbook of Postpartum Hemorrhage, 2nd Edition. Sapiens London.

Flood K.M., Saidd S., Geary M., robson M., Fitzpatrick C., Malone F.D. 2009. Changing trends in peripartum hysterectomy over the last 4 decades. *Am J Obstet Gynecol*, 200, 632. e1-632.e6.

Fong A., Wu E., Chung J.H., and Ogunyemi D.A. 2014. Temporal trends iand morbidities of vacuum, forceps and combined use of both. J Matern Fetal Neonatal Med doi: 10.3109/1476058.2014.904282 downloaded 23/04/2014.

Fong A., Leakek J., Pan D., and Ogunyemi D. 2010. Demographic, institutional and obstetric risk factors for postpartum haemorrhage mortality. *J Obstet Gynaecol,* 30 (5), 470-5.

Food and Drug Administration. 2002. General Principles of Software Validation; Final Gudence for Industry and FDA Staff, *FDA*, Rockville, MA>

Food and Drug Administration. 1999. Guidence for Industry- Compertierised Systems Used in Clinical Trials. *FDA* Rockville, MD.

Ford J.B., Shand A.W., and Roberts C.L. 2013. Characteristics, causes and treatment of postpartum haemorrhage in first and second pregnancies. *Australian and New Zealand Journal of Obstetrics and Gynaecology,* 53 (1), 90-3.

Ford J.B., Algert C.S., Kok C., Choy M.A., and Roberts C.L. 2012. Hospital data reporting on postpartum hemorrhage: under-estimates recurrence and over-estimates, the contribution of uterine atony. *Maternal and Child Health Journal,* 16 (7), 1542-8.

Ford J.B., Roberts C. L., Simpson J., Vaughan J. and Cameron C.A. 2007a. Increased postpartum hemorrhage rates in Australia. *International Journal of Gynaecology & Obstetrics,* 98**,** 237-243.

Ford J.B., Roberts C. L., Bell J.C., Algert C.S. and Morris J.M. 2007b. Postpartum haemorrhage occurrence and recurrence: a population-based study. *Medical Journal of Australia,* 187**,** 391-3.

Fraser W.D., Marcoux S., Krauss I., Douglas J., Goulet C., and Boulvain M for the PEOPLE (Pushing early or pushing late with epidural) Study Group. 2000. Multicenter, randomised, controlled trial of delayed pushing for nulliparous women in the second stage of labor with continuous epidural analgesia. *AmJOG*, 182, 1165-72.

Freund J., Meiman J., Kraus C. 2013. Using electronic medical records data to characterise the level of medication use by age-groups in a network of primary care clinics. J Prim Care Community Health, 4 (4), 286-93

Fry J. 2007. Physiological third stage of labour: support it or lose it. *British Journal of Midwifery,* 15**,** 693-695.

Fyfe E.M., Thompson J.M., Anderson N.H., Groom K.M., and McGowan L.M. 2012. Maternal obesity and postpartum haemorrhage after vaginal and caesarean delivery among nulliparous women at term: a retrospective cohort study. *BMC Pregnancy & Childbirth,* 12, 112.

Gahres E.E., Albert S. N. and Dodek S.M., 1962. Intrapartum blood loss measured with Cr 51-tagged erythrocytes. *Obstet Gynaecol,* 19**,** 455-62.

Gai M-Y., Wu L-F., Su Q-F., Tatsumato K. 2004. Clinical observarion of blood loss reduced by tranexamic acid during and after caesarean section: a multi-center, randomised trial. *Eur J Obset Gynecol Reprod Biol*, 112, 154-7.

Gamble J.A., Creedy D. K., Webster J. and Moyle W. 2002. A review of the literature on debriefing or non-directive counselling to prevent postpartum emotional distress. *Midwifery,* 18**,** 72-9.

Gardosi J., Figueras F., Clausson B., and Francis A. 2011. The customised growth potential: an international research tool to study the epidemiology of fetal growth. *Paediatric Perinatal Epidemiology,* 25**,** 2-10.

Garland D. and Jones K. 1994. *Preliminary evaluation of hydrotherapy in labour, using hard indicators*.

Ge J., Liao H., Duan L., Wei Q., and Zeng W. 2012. Uterine packing during cesaran section in the management of intractable hemorrhage in central placenta praevia. *Arch Gynecol Obstet*, 285, 285-9.

Geller S.E., Rosenberg D., Cox S., Brown M., Simpson L., and Kilpatrick S. 2004. A scoring system identified near-miss maternal morbidity during pregnancy. *J Clin Epidemiol* 57, 716-20.

Geoghegan J., Daniels J., Moore P., Thompson P., Khan K. and Gulmezoglu M.A. 2009. Cell salvage at caesarean section: the need for an evidence-based approach. *BJOG: An International Journal of Obstetrics & Gynaecology,* 116**,** 743-747.

Georgiou C. 2009. Balloon tamponade in the management of postpartum haemorrhage: a review. *BJOG*, 116, 748-57.

Gharoro E.P. and Enabudoso. E. J. 2009. Relationship between visually estimated blood loss at delivery and postpartum change in haematocrit. *J Obstet Gynaecol,* 29**,** 517-20.

Gilbert L., Porter W. and Brown V.A., 1987. Postpartum haemorrhage: a continuing problem. *BJOG,* 94**,** 67-71.

Gill L. 1997. OX-LINK: The Oxford medical record linkage system. Iln: *Record Linkage Techniques*, 15-33. Washington D.C., National Academy Press.

Giutellaelli O. 2012. Why does the health of immigrants deteriorate? *PhD Thesis*, Boston University, Institute for Economic Development, Boston, USA.

Glaze S., Ekwalanga P., Roberts G., Lange I., Birch C., Rosengarten A., Jarrell J. and Ross S. 2008. Peripartum hysterectomy: 1999 to 2006. *Obstetrics & Gynecology,* 111**,** 732-738.

Glaser B.G. and Strauss A.L. 1967. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. New York. Aldine Publishing.

Glazener C.M.A., MacArthur C. and Garcia J. 1993. Postnatal care: time for a change. *Contemporary Reviews in Obstetrics and Gynaecology,* 5**,** 130-6.

Glinianaia S.V., Rankin J., Pless-Mullolit., Pearce M.S., Charlton M. and Parker L. 2008. Temporal changes in key maternal and fetal factors affecting birth outcomes: A 32-year population-based study in an industrial city. *BMC Pregnancy & Childbirth,* 8.

Glover P. 2006. Blood loss at delivery: how accurate is your estimation? *Australian Midwifery,* 16**,** 21-4.

Goddard M and Smith P. 2001. Equity of access to health care services: Theory and evidence from the UK. *Social Science & Medicine*, 53, 1149-62.

Government of South Australia. 2012. Perinatal Practice Guidelines, Section 1, Chapter 11: Postpartum Haemorrhage.*Maternity Care in SA.*

Green B.N., Johnson C.D., and Adams A. 2001. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *J Sports Chiropr Rehabil*, 15, 5-19.

Greenwell E.A., Wyshak G., Ringer S.A., Johnson L.C., Rivkin M.J., and Lieberman E. 2012 Intrapartum Temperature Elevation, Epidural Use, and Adverse Outcome in Term Infants. *PEDIATRICS,* 129**,** e447-e454.

Gregory K.D., Henry O. A., Ramicone E., Chan L.S., Platt L.D 1998. Maternal and Infant Complications in High and Normal Weight Infants by Method of Delivery. *Obstet Gynaecol,* 92**,** 507-13.

Griffiths P., and Norman I. 2005. Science and art of reviewing the literature. *Int J Nursing Studies*, 42, 373-6.

Grotegut C. A., Paglia M. J., Johnson L. N., Thames B. and James A. H. 2011. Oxytocin exposure during labor among women with postpartum hemorrhage secondary to uterine atony. *American Journal of Obstetrics and Gynecology,* 204**,** 56 e1-6.

Guendelman S., Thornton D., Gould J. and Hosang N. 2006. Obstetric complications during labor and delivery: assessing ethnic differences in California. *Women's health issues : official publication of the Jacobs Institute of Women's Health,* 16**,** 189-97.

Gulmezoglu A. M. and Souza J. P. 2009. The evolving management of the third stage of labour. *BJOG: An International Journal of Obstetrics & Gynaecology,* 116**,** 26-28.

Gulmezoglu A.M., Forna F., Villar J., and Hofmeyr G.J. 2007. Prostaglandins for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews,* Issue 3, CD000494.

Gulmezoglu A.M., Villar J., Nhu Ngoc N.T., Iaggio G., Carroli G., Adetoro L., Abdel-Aleem H., Cheng L., Hofmeyr G.J., Lumbiganon P., Unger C., Prendiville W., Pinol A., Elbourne D., El-Rafaey H., and Schulz F.F. 2001. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. *Lancet,* 358**,** 689-95.

Gurtani F.M., Fadaek B., and Akbaru M. 2013. Emergency peripartum hysterectomy in Isfahan: maternal mortality and morbidity rates among the women who underwent peripartum hysterectomy. *Advanced Biomedical Research*, 2, 20.

Gyte G. 2006. NCT Evidence Based Briefing Third Stage of Labour. *NewDigest,* 35, 24-8.

Gyte G. 1992. The significance of blood loss at delivery. *MIDIRS Midwifery Digest*, 2 (1), 88-92.

Habek D., and Becarevic R. 2007. Emergency Periartum Hysterectomy in a Tertiary Obstetric Center: 8 year evaluation. *Fetal Diagn Ther*, 22, 139-42.

Hackshaw A. 2009. A Concise Guide to Clinical Trials.Chapter 1, fundamental concepts. *BMJ Books*, Wiley-Blackwell, Chichester.

Hall M.H. 2001. Near misses and severe maternal morbidity. Why Mothers Die 1997-1999. Report of the Confidential Enquiry into Maternal Deaths in the United Kingdom, London, RCOG.

Hall M.H., Halliwell R., Carr-Hill R. 1985. Concomitant and repeated happenings of complications in the third stage of labour. *BJOG,* 92**,** 732-8.

Hammond K.W., Helbig S.T., Benson C.C., and Braithwaite-Skeptoe B.M. 2003. Are electronic medical records trustworthy? Observations on copying, pasting and duplication. Annual Symposium Proceedings, AMIA Symposium, 269-73. Washington USA.

Handelsman D. 2010. Electronic data capture: when will it replace paper? SAS Inc www.sas.com Accessed 18/06/2014.

Hannah M.E., Hannah W. J., Hewson S.A., Hodnett E.D., Saigal S., Willan A.R., Term Breech Collaborative. 2000. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. *Lancet,* 356**,** 1375-83.

Harper M., Dugan E., Espeland M.A., Martinez-Borges A., and McQuellon C. 2007. Why African-American women are at greater risk for pregnancy-related death. *Ann Epidemiol,* 17, 180-5.

Harper Bulman K., and McCourt C. 2002. Somali refugee women's experiences of maternity care in west London: A case study, *Critical Public Health*, 12 (4), 365-80.

Harris T., Munro J., and Jokinen M. 2012. Practice Guideline 15: Third stage of Labour. London: Royal College of Midwives.

Hart D.B. 1912. Guide to Midwifery. London, Heinemann, p220.

Hayashi R.H. 1990. The role of prostaglandins in the treatment of postpartum haemorrhage. *J Obstet Gynaecol,* 10**,** S2104.

Hayman R.G., Arulkumaran S and Steer P.J. 2002. Uterine compression sutures: Surgial management of postpartum haemorrhage. *Obstet Gynecol* 99, 502-6.

Haynes C.L., Cook G.A., and Jones M.A. 2007. Legal and ethical considerations in processing patient-identifiable data without patient consent: lessons learnt from developing a disease register. *J Med Ethics*, 33, 302-7.

Hazra S., CHilaka V.N., Rajendran S., and Konje J.C. 2004. Massive postpartum haemorrhage as a cause of maternal morbidity in a large tertiary hospital. *Journal of Obstetrics and Gynaecology,* 24 (5), 519-29.

Health Research Authority 2012. Do I need NHS REC approval? (*www.hra-decisiontools.org.uk*). Accessed 16/06/2014.

Henry A., Birch M., Sullivan E. A., Katz S. and Wang Y. A. 2005. Primary postpartum haemorrhage in an Australian tertiary hospital: a case-control study. *Australian & New Zealand Journal of Obstetrics & Gynaecology,* 45**,** 233-236.

Hernan M.A., Hermandez-Diaz S., Werler M.M., and Mitchell A.A., 2002. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol,* 155**,** 176-84.

HESonline. 2009. Table 7: Method of onset of labour 2008-09. Health and Social Care Information Centre, *www.hscic.giv.uk/hes* accessed 23/10/2013.

Hester J.D., 1975. Postpartum hemorrhage and reevaluation of uterine packing, *Obstet Gynecol,* 45, 501-4.

Heslehurst N., Rankin J., Wilkinson J.R., and Summerbell C.D. 2010. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619,323 births, 1988- 2007. *International Journal of Obesity,* 34, 420-8.

Higgins J.P.T., and Green S. 2008. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.1 Cochrane Book Series, John Wiley & Sons Ltd, London. (latest version, 5.1.0 www.cochrane.org/training/cochrane-handbook downloaded 06/05/2014.

Higgins P. G. 1982. Measuring nurses' accuracy of estimating blood loss. *Journal of advanced nursing,* 7**,** 157-62.

Hill K., Thomas K., AbouZahr C., Walker N., Say L., Inoue M., Suzuki E on behalf of the Maternal Mortality Workshop. 2007. Estimates of maternal morbidity worldwide between 1990 and 2005: an estimate of available data. *Lancet,* 370**,** 1311-9.

Hinshaw K., Simpson S., Hildreth A. and Thornton J. 2008. A randomised controlled trial of early versus delayed oxytocin augmentation to treat primary dysfunctional labour in nulliparous women. *BJOG,* 115**,** 1289-95.

HL7 International. 2010. Unlocking the power of health information. *HL7 Annual Report*. wwwhl7.org/documentcenter Accessed 18/06/2014.

HMGovernment. 2012. English indices of deprivation. *Communities and Local Government,* London

HMSO. 1998. *Data Protection Act* [Online]. The Stationary Office. Available: http://www.legislation.gov.uk/ukpga/1998/29 [Accessed 13/09/2012 2012].

Hofmeyr G.J., Abdel-Aleem H., and Abdel-Aleem M.A. 2013. Uterine massage for preventing postpartum haeomrrhage. *Cochrane Database of Systematic Reviews*, 7 CD006431

Hofmeyr G.J., Abdel-Aleem H., and Abdel-Aleem M.A. 2008. Uterine massage for preventing postpartum haemorrhage. *Cochrane Database of Sysemtatic Reviews* 2008, Issue 3. Art. No.: CD006431. DOI: 10.1002/14651858.CD006431.pub2.

Hofmeyr G.J. 2001. Induction of labour with misoprostol. *Curr Opin Obstet Gynecol,* 13**,** 577-81.

Hogan M.C., Foreman K.J., Naghavi M., Ahn S.J., Wang M., Makela S.M., Lopez A.D., Lozano R., and Murray C.J.L. 2010 Maternal mortality in 181 countries, 1980-2008: a systematic analysis of progress towards Millenium Development Goal 5. *The Lancet,* 375 (9726), 1609-23.

Hollowell J., Puddicombe D., Rowe R., Linsell L., Hardy P., Stewart M., Maggie Redshaw M., Newburn M., McCourt C., Sandall J., MacFarlane A., Silverton L., Brocklehurst P., on behalf of the Birthplace in England Collaborative Group. 2011. The Birthplace national prospective cohort study: perinatal and maternal outcomes by planned place of birth. Birthplace in England research programme. Final report part 4. London: NIHR Service Delivery and Organisation programme; 2011.

Holm C., Langhoff-Roos J., Petersen K.B., Norgaard A., and Diness B.R. 2012. Severe postpartum haemorrhage and mode of delivery: a retrospective cohort study, *BJOG,* 119 (5), 596-604.

Homer C. S. E., Kurinczuk J. J., Spark P., Brocklehurst P., and Knight M. 2010. A novel use of a classification system to audit severe maternal morbidity. *Midwifery,* 26**,** 532-536.

HSCIC. 2013. Maternity data set. *Health & Social Care Information Centre,* www.hscic.giv.uk/maternityandchildren/maternity Accessed 30/10/2013.

Huber P.J. 1967. *Behaviour of liklihood estimates under non-standard conditions*, University of California Press.

Humphrey M. 2003. Is grand multiparity an independent predictor of pregnancy risk? A retrospective observational study. *Medical Journal of Australia,* 179**,** 294-6.

Humphrey T., and Tucker J. S. 2009. Rising rates of obstetric interventions: exploring the determinants of induction of labour. *Journal of Public Health,* 31**,** 88-94.

Huq F.Y., and Kadir R.A. 2011. Management of pregnancy, labour and delivery in women with inherited bleeding disorders. *Haemophilia,* 17 Suppl 1, 20-30.

Hutton E.K., and Hassan E.S. 2007 Late vs early Clamping of the Umbilical Cord in Full-term Neonates. *JAMA*, 297 (11), 1241-52.

Ibrahim M. I., Raafat T. A., Ellaithy M. I., and Aly R. T. 2013. Risk of postpartum uterine synechiae following uterine compression suturing during postpartum haemorrhage. *The Australian & New Zealand journal of obstetrics & gynaecology,* 53**,** 37-45.

ICNARC 2009. Female admissions (aged 16-50 years) to adult, general critical care units in England, Wales and Northern Ireland, reported as "currently pregnant" or "recently pregnant" Jan 2005-Dec 2007. Intensive Care National Audit and Research Committee.

Iedema R., Jorm C., Lond D., Brathwaite J., Travaglia J., and Westbrook M. 2006. Turning the medical gaze upon itself: Root cause analysis and the investigation of clinical error. *Social Science and Medicine*. 62, 1605-15.

Inch S. 1988. Physiology of third Stage of Labour. *Midwives Chronicle and Nursing Notes,* 101**,** 42-43.

Iveson A., Liddell K., Fear N., Hotopf S., and Wessely S. 2006. Consent, confidentiality, and the Data Protection Act. *BMJ*, 332, 165-9

Jakobsson M., Gissler M., and Tapper A-M., 2012. Risk factors for vlood transfusion at delivery in Finland. *Acta Obstet Gynecol Scand*, 92 (4), 414-20.

James A.H. 2006. Von Willebrand Disease. *Obstetrical and Gynecological Survey,* 61**,** 136- 145.

Jansen A.J.G., van Rhenen D.J., Steegers E.A.P., and Duvekot J.J. 2005. Post[artum Hemorrhage and transfusion of Blood and Blood Components. *Obstetical & Gynecological Survey*, 60 (10), 663-71.

Jayaweera H. 2011. Briefing: Health of Migrants in the UK: What Do We Know? *The Migration Observatory,* wwwmigrationobservatory.ox.ac.uk Accessed 23/10/2013.

Jin R., Gui Y., and Chen Y. 2014. Risk factors associated with mergency peripartum hysterectomy. *Chinese Medcial Journal*, 127 (5), 900-4.

Johansen E. and Bathija H. 2008. Effects of female genital mutilation on childbirth in Africa. *WHO Policy Brief*.

Johanson R.B., Menon V., Burns E., Kargramanya E., Osipov V., Israelyan M., Sargsyan K., Dobson S., and Jones P. 2002. Managing Obstetric Emergencies and Trauma (MOET) structured skills training in Armenia, utilising models and reality based scenarios. *BMC Medical Education,* 2.

Jokinen M. and Munroe. J. 2008. Evidence based Guidelines for Midwifery-Led Care in Labour 4th edition. London: RCM Trust.

Jolley S. 2009. An overview of uterine fibroids. *Nursing Standard,* 24**,** 44-8.

Jolly M.C., Sebire N. J., Harris J.P., Regan L. and Robinson S. 2003. Risk factors for macrosomia and its clincial consequence: a study of 350,311 pregnancies. *Eur J Obstet Gynecol Reprod Biol,* 111**,** 9-14.

Jones B., Zhang E., Alzouebi A., Robbins T., Paterson-Brown S., Prior T., and Kumar S. 2013. Maternal and prinatal outocmes following peripartum hysterectomy from a single tertiary centre. *Aus NZ J Obstet Gynaecol*, 53,6, 561-5.

Jonsson A. and Halabi J. 2006. Work related post-traumatic stress as described by Jordanian emergency nurses. *Accid Emerg Nurs,* 14 (2), 89-96.

Joseph K. S., Rouleau J., Kramer M. S., Young D. C., Liston R. M. and Baskett T. F. 2007. Investigation of an increase in postpartum haemorrhage in Canada. *BJOG: An International Journal of Obstetrics & Gynaecology,* 114**,** 751-759.

Jou H-J., Hung H-W., Ling P-Y., Chen S-M., and Wu S-C. 2008. Peripartum hysterectomy in Taiwan. *Int J Gynecol Obstet*, 101, 269-72.

Jozwiak M., Oude Rengerink K., Benthem M., van Beek E., Dijksterhuis M.G.K., de Graaf I.M., van Huizen M.E., Oudijk M.A., Papatsonis D.N.M., Perquin D.A.M., Porath M., van der Post J.A.M., Rijnders R.J.P., Scheepers H.C.J., Spaanderman M.E.A., van Pampus M.G., de Leeuw J.W., Mol B.W.J., and Bloemenkamp K.W.M., for the PROBAAT Study Group. 2011. Foley catheter versus baginal prostaglandin E2 gel for induction of labour at term (PROBAAT trial): an open-label, randomised controlled trial. *Lancet*, 378 (9809), 2095-2103

Kallen B. 2008. Maternal morbidity and mortality in in-vitro fertilization. *Best Practice and Research Clinical Obstetrics and Gynaecology,* 22**,** 549-58.

Kara M. 2012. Emergency peripartun hysterectomy cases in Agri: a 6 year review. *Clin Exp Obstet Gynecol*, 39 (2), 202-4.

Karayalcin R., Ozcab S., Ozyer S., Mollamahmutoglu L., and Danisman N. 2011. Emergency peripartum hysterectomy. *Arch Gynecol Obstet*, 283 (4), 723-7.

Karoshi M. 2010. The B-Lynch uterine brace suture, and a bit of this and a bit of that... *International Journal of Gynaecology & Obstetrics,* 108**,** 184-6.

Kastner E.S., Figueroa R., Garry D., and Maulik D. 2002. Emergency peripartum hysterectomy: experience at a community teaching hospital. *Obstet Gynecol*, 99 (6), 971-5.

Katesmark M., Brown R., and Raju K.S. 1994. Successful use of a Sengstaken-Blakemore tube to control massive postpartum haemorrhage. *BJOG,* 101, 259-60.

Kavle J.A., Khalfan S.S., Stoltzfus R.J., Witter F., Tielsch J.M. and Caulfield L.E. 2006. Measurement of blood loss at childbirth and postpartum. *International Journal of Gynecolgy & Obstetrics,* 95**,** 24-8.

Kavle J.A., Stoltzfus R. J., Witter F., Tielsch J.M., Khalfan S.S., and Caulfield L.E. 2008. Association between Anaemia during Pregnancy and Blood Loss at and after Delivery among Women with Vaginal Births in Pemba Island, Zanzibar, Tanzania. *J Health Popul Nutr,* 26**,** 232-40.

Kayabasoglu F., Guzin K., Aydogdu S., Sezginsoy S., Turkgeldi L., and Gunduz G., Emergency peripartum hysterectomy in a tertiary Istanbu hospital. *Arch Gynecol Obstet*, 278 (3), 251-6.

Keizer J.L., Zwart J. J., Meerman R.H., Harinck B.I.J., Feuth H.D.M., and van Roosemalen J. 2006. Obstetric intensive care admissions: A 12- year review in a tertiary care centre. *Eur J Obstet Gynecol Reprod Biol,* 128**,** 152-6.

Kenyon A.P., and Bewley S. 2009. The effect of age on obstetric (maternal and fetal) outcomes. Series Editor: Bewley S., Ledger W., Nickolou D., Kehoe S. *Reproductive Ageing,* 125-40. London, RCOG Press.

Kenyon A.P., Nelson-.Piercy C., Girling J., Williamson C., Tribe R.M. and Shennan A.H. 2002. Obstetric cholestasis, outcome with active management: a series of 70 cases. *BJOG,* 109**,** 282-8.

Kenyon S.L., Taylor D.J., and Tarnow-Mordi W. 2001. Broad-spectrum antibiotics for spontaneous preterm labour: the ORACLE II randomised trial. *The Lancet,* 357 (9261), 989-94.

Keriakos R., and Chaudhuri S. 2012. Operative interventions in the management of majorpostpartum haemorrhage. *J Obstet Gynaecol,* 32, 14-25.

Keriakos R., and Mukhopadhyay A. 2006. The use if the Rusch balloon for management of severe postpartum haemorrhage. *J Obstet Gynecol*, 26, 335-8.

Kershaw K. 2007. Adverse clinical incidents:Support for Midwives. *Midwives.* 10 (10), 463-5.

Khan B., Khan B., Sultana R., Bashir R., and Deeba F. 2012. A ten year review od emergency peripartum hysterectomy in a tertiary care hospital. *J Ayub Med Coll Abbottabad*, 24 (1), 14-7.

Khan K.S., Wojdyla D., Say L., Gulmezoglu A.M. and van Look P.F.A. 2006. WHO analysis of causes of maternal death: a systematic review. *The Lancet,* 367**,** 1066- 74.

Kiesewetter B., and Lehner R. 2012. Maternal outcome monitoring: induction of labor versus spontaneous onset of labor- a retrospective data analysis. *Arhchives of Gynecology and Obstetrics,* 286 (1), 37-41.

Kimmel A.J. 1988. Ethics and Values in Applied Social Research. p 42-50. Newbury Park CA, Sage

Kirtava A., Drews C., Lally C., Dilley A., and Evatt B. 2003. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand's disease receiving care in haemophilia treatment centrs: a case-control study. *Haemophillia*, 9, 292-7.

Kish L. 1965. *Survey sampling,* New York, Wiley.

Kitsantas P., and Christopher K.E. 2013. Smoking and Respiratory Conditions in Pregnancy: Associations with Adverse Pregnancy Outcomes. *Southern Medical Journal,* 106 (5), 310-5.

Kiuchi T., and Kaihara S. 1997. Automated generation of a World Wide Web-based data entry and check program for medical applications. *Comput Methods Programs Biomed*. 52 (2), 129-38

Knight M., Kurinczuk J.J., Tuffnell D., and Brocklehurst P. 2005. The UK Obstetric Surveillance System for rare disorders of pregnancy. *BJOG*, 112, 263-5.

Knight M., on behalf of UKOSS. 2007. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. *BJOG: An International Journal of Obstetrics and Gynaecology,* 114**,** 1380-1387.

Knight M, Callaghan W. M., Berg C, Alexander S, Bouvier-Colle MH., Ford J. B, Joseph K. S., Lewis G, Liston R. M, Roberts C. L, Oats J. and Walker J. 2009. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. *BMC Pregnancy & Childbirth,* 9**,** 55.

Knight M., Kurinczuk J.J., Spark P., and Brocklehurst P. 2009. Inequalities in maternal health: cohort study of ethnic variation in severe maternal morbidities. *BM,J* 338, b542 doi: 10.1136/bmj.b542

Knight M., Kurinczuk J., Spark P., and Brocklehurst P. 2010. Emergency Postpartum Hysterectomy for Uncontrolled Postpartum Bleeding: a systematic review. *Obstet Gynecol*, 116 (6), 1306-7.

Kodkany B., and Derman R. 2006. Pitfalls in assessing blood loss and decision to transfer In: *A Textbook of Postpartum Hemorrhage* Sapiens Publishing.

Kominiarek M. A. and Kilpatrick S. J. 2007. Postpartum hemorrhage: a recurring pregnancy complication. *Seminars in Perinatology,* 31**,** 159-166.

Korn E.L., and Graubard B. I., 1999. *Analysis of Health Surveys,* New York, Wiley.

Kovavisarch E., and Kosolkittiwong S. 1997. Bimanual uterine compression as a major technique in controlling severe postpartum hemorrhage from uterine atony. *Journal of the Medical Association of Thailand,* 80.**,** 266–269.

Kramer M.S., Berg C., Abenhaim H., Dahhou M., Rouleau J.,Mehrabadi A., and Joseph K.S. 2013. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. *Am J Obstet Gynecol,* 209 (5), 449.e1-449.e7.

Kramer M.S., Dahhou M., Vallerand D., Liston R., and Joseph K.S. 2011. Risk factors for postpartum hemorrhage: can we explain the recent temporal increase? *JOGC,* 33 (8), 810-9.

Kreuter F., and Valliant R. 2007. A survey on survey statistics: what is done and can be done in Stata. *Stata Journal,* 7**,** 1-21.

Kuhn T.S.1972. *Scientific paradigms, in B.Barnes (ed). Sociology of Science: selected readings.* Harmondsworth. Penguin.

Kush R., Bleicher P., Kubick W., Kush S., Marks R. and Raymond S. 2003. eClinical Trials: Planning and Implementation. Boston MA, Thomson CenterWatch.

Kwee A., Botts M.L., Visser G.H.A. and Bruinse H.W. 2006. Emergency peripartum hysterectomy: A prospective study in The Netherlands. *Eur J Obstet Gynecol Reprod Biol,* 124**,** 187-92.

Laas E., Bui C., Popowski T., Matondo Mbaku O., and Rozenberg P. 2012. Trends in the rate of invasive procedures after the addition of intrauterine tamponade test to a protocol for management of severe postpartum hemorrhage. *Am J Obstet Gynecol*, 207 (281), e1-7

Lalonde A., Daviss B., Acosta A., and Herschderfer K. 2006. Postpartum hemorrhage today: ICM/FIGO initiative 2004-2006. *International Journal of Gynaecology & Obstetrics,* 94, 243-53.

Langdana F., Geary M., Haw W., and Keane D. 2001. Peripartum hysterectomy in the 1990s: any new lessons? *J Obstet Gynaecol* 21 (2): 121-3.

Laraia B.A., Siega-Riz A.M., Gundersen C., and Dole N. 2006. Psychoscial Factors and Socioecomonic indicators are Assosiated with Household Food Insecurity in Pregnant Women. *J Nutr* 136, 177-82.

Larsson C., Saltvedt S., Wiklund I., Pahlen S., and Andolf E. 2006. Estimation of blood loss after cesarean section and vaginal delivery has low validity with a tendency to exaggeration. *Acta Obstet Gynecol Scand,* 85**,** 1448-1452.

Lathrop A., Winningham B. and van de Vusse L. 2007. Simulation-based learning for midwives: background and pilot implementation. *J Midwifery Womens Health,* 52**,** 492-8.

Laughlin S.K., Baird D.D., Savitz D.A., Herring A.H. and Hartmann K.E. 2009. Prevalence of Uterine Leiomyomas in the First Trimester of Pregnancy. *Obstet Gynecol,* 113 (3), 630-5.

Lawton R., and Parker D. 2002. Barriers to incident reporting in a healthcare system. *Quality &Safety in Health Care.*11, 15-8.

Leduc D., Senikas V., Lalonde A.B., Ballerman C., Biringer A., Delaney M., Duperron L., Girard I., Jones D., Lee L.S., Shephers D., Wilson K., Clinical Practice Obstetrics Committee, Society of Obstetricians and Gynaecologists of Canada. 2009. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *JOGC*, 31 (10), 980-93.

Lee C.A., Chi C., Pavord S.R., Bolton- Maggs P.H.B., Pollard D., Hinchcliffr-Wood A., and Kadir R.A. 2006. The obstetric and gynaecological management of women with inherited bleeding disorders- review with guidelines produced by a taskforce of UK Haemophilia Centre Doctors' Organization. *Haemophilia,* 12**,** 301 -36.

Lee I.H., Son J.H., Shin Y.C., Byun J.H., Yoon H.J., and Jee Y.S. 2012. Anesthetic review of emergency peripartum hysterectomy following vaginal and cesarean delivery: a retrospective study. *Korean Journal of Anesthesiology*, 63 (1), 43-7.

Lemmens H.J., Bernstein D. P. and Brodsky J.B. 2006. Estimating blood volume in obese and morbidly obese pateints. *Obesity Surgery,* 16**,** 773-6.

Lennox C., and Marr L. 2011. Scottish Confidential Audit of Severe Maternal Morbidity 7th Annual Report (Data from 2009). Health Improvement Scotland.

Lennnox C., and Marr L. 2012. Scottish Confidential Audit of Severe Maternal Morbidity 8th Annual Report (Data from 2010). Healthcare Improvement Scotland 2012

Lennox C.,and Marr L. 2013. Scottish Audit of Severe Maternal Morbidity: reducing avoidable harm: 9th Annual Report. Edinburgh: Health Improvement Scotland.

Lennox C., on behalf of SPERCH. 2007. Scottish Confidential Audit of Severe Maternal Morbidity: 5th Annual Report. Edinburgh: NHS Scotland.

Lennox C. and Marr L. 2010. Scottish Audit of SEvere Maternal Morbidity 6th Annual Report 2008.

Levine R.J. 2000. Some recent developments in the International Guidelines on the Ethics of Research Involving Human Subjects. *Ann NY Acad Sci* 918, 170-7.

Lewis G. (Ed) 2007a. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2003-2005. Summary and Key Recommendations for Midwives. London: CEMACH.

Lewis G. (Ed) 2007b. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer- 2003-2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. RCOG, London

Lewis G. (Ed) 2003. Why Mother's Die 2000-2002. Confidential Enquiry into Maternal and Child Health (CEMACH): Improving care for mothers, babies and children. 6th Annual Report of Confidential Enquiries into Maternal Deaths in the United Kingdom. RCOG London

Lewis G., Drife J., and Botting B.1998. Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdon 1994-1996. London: CEMD.

Lewis L.N., Hickey M., Doherty D.A., and Skinner S.R. 2009. Why do pregnancy outcomes differ in teenage mothers? A Western Australian study. *Medical Journal of Australia,* 190 (10), 537-41.

Liabsuetrakul T., Choobun T., Peeyananjarassri K., and Islam Q.M. 2007. Prophylactic use of ergot alkaloids in the third stage of labour. *Cochrane Database of Systematic Reviews*, Issue 2, CD005456

Lieberman E., Lang J.M., Frigolette F., Richardson D.K., Ringers S.A. and Cohen A. 1997 Epidural Analgesia, Intrapartum Fever, and Neonatal Sepsis Evaluation. *PEDIATRICS,* 99**,** 415-9.

Lim S.K. 1994. A study to compare midwives' visual estimation of blood loss in "water" and on "land". MSc Dissertation, University of Surry, School of Nursing and Midwifery.

Litchfield J., Freeman J., Schou H., Elsley M., Fuller R., and Chubb B. 2005. Is the future for clinical trials internet-based? A cluster randomised clinical trial. *Clin Trials* 2 (1), 72-9.

Liu S., Joseph K.S., Bartholomew S., Fahey L., Lee L., Allen A.C., Kramer M.S., Sauve R., Young D.C., Liston R.M., Maternal Health Study Group of the Canadian Perinatal Surveillance. 2010. Temporal trends and regional variations in severe maternal morbidity in Canada, 2003-2007, *J Obstet Gynaecol*, 32 (9), 847-55.

Lucas M. 2006. Reflections on the third stage. *The Practising Midwife*, 9 (6), 30-1.

Luegenbiehl D.L., Brophy G.H., Artigue G.S., Phillips K.E. and Flak R.J. 1990. Standardiized Assessment of Blood Loss. *MCN- American Journal of Maternal and Child Nursing,* 15**,** 241-4.

Lutomski J.E., Greene R.A., and Byrne B.M. 2012. Severe maternal mobidity during childbirth hospitalisation: a comparative analysis between the Republic of Ireland and Australia. *Eur J Obstet Gynecol Reprod Bio*, 163, 148-53.

Lutomski J.S., Byrne B.M., Devane D., and Greene R.A. 2012. Increasing trends in atonic postpartum haemorrhage in Ireland: an 11-year population-based cohort study. *BJOG,* 119 (3), 306-14.

Lyndon A., Lee H.C., Gilbert W.M., Gould J.B., and Lee K.A. 2012. Maternal morbidity during childbirth hospitalization in California, *The Journal of Maternal-Fetal & Neonatal Medicine,* 25 (12), 2529-35.

Lyndon A., Lagrew D., Shields L., Melsop K., Bingham B., and Main E (Eds). 2010. Improving Health Crae Response to Obstetric Hemorrhage. (California Maternal Quality Care Collaborative Toolkit to Transform Maternity Care) Developed under contract #08-85012 with the California Department of Public Health; Maternal, Child and Adolescent Health Division; Published by the California Maternal Quality Care Collaborative.

Lyons J. 1999. Reflective education for professional practice: discovering knowledge from experience. *Nurse Education Today,* 19**,** 29-34.

MacPhail S. and Fitzgerald J. 2001. Massive post-partum haemorrhage. *Current Obstetrics and Gynaecology,* 11**,** 108-114.

Magann E.F., Doherty D.A., Sandin A.T., Chauhan S.P., and Morrison J.C. 2013. The effects of an increasing gradient of maternal obesity on pregnancy outcomes. *Aust NZ J Obstet Gynaecol,* 53 (3), 250-7.

Magann E.F., Doherty D. A., Briery C.M., Niederhauser A., Chauhan S.P. and Morrison J.C. 2008. Obstetric characteristics for a Prolonged Third Stage of Labour and Risk for Postpartum Hemorrhage. *Gynecol Obstet Invest,* 65**,** 201-5.

Magann E.F., Evans S., Hutchinson M., Collins R., Lanneau G. and Morrison J.C., 2006. Postpartum Hemorrhage After Cesarean Delivery: An Analysis of Risk Factors. *Southern Medical Journal,* 98**,** 681--685.

Magann E.F., Doherty D.A., Briery C.M., Niederhause A., and Morrison J.C. 2006b. Timing of placental delivery to prevent post-partum haemorrhage. Lessons learnt from an abandoned randomised clinical trial. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 46, 549-51.

Magann E.F., Evans S., Hutchinson M., Collins R., Howard B., and Morrison J.C. 2005. Postpartum Hemorrhage Afer Vaginal Birth: An Analysis of Risk Factors. *Southern Medical Journal,* 98 (4), 419-22.

Magann E.F., Evans S., Chauhan S.P., Lanneau G., Fisk A.D., and Morrison J.C. 2005. The Length of the Third Stage of Labor and the Risk of Postpartum Hemorrhage. *AmJOG*, 105 (2), 290-3.

Majoko F., Nystrom L., and Lindmark G. 2002. No benefit, but increased harm from high dose (100µg) misoprostol for induction of labour: a randomised trial of high vs. low (50µg) dose misoprostol. *Journal of Obsterics and Gynaecology,* 22**,** 614-7.

Malabarey O., Almog B., Brown R., Abenhaim H. A., and Shrim A. 2011. Postpartum hemorrhage in low risk population. *Journal of Perinatal Medicine,* 39**,** 495-498.

Mantel G.D., Buchmann E., Rees H. and Pattinson R.C.1998. Severe acute maternal morbidity: a pilot study of a definition for a near-miss. *BJOG: An International Journal of Obstetrics & Gynaecology,* 105**,** 985-90.

Mantel G.D.M., and Moodley J. 2002. Can a developed country's maternal mortality review be used as the 'gold standard' for a developing country? *European Journal of Obstetrics and Gynecology and Reproductive Biology,* 100**,** 189-195.

Marcovici I., and Scoccia B. 1999. Postpartum hemorrhage and intrauterine balloon tamponade. *J Reprod Med*, 44, 122-6.

Maresh M., Dawson A.M., and Beard R.W. 1986. Assessment of an on-line computerized perinatal data collection and information system. *BJOG,* 93, 1239-45.

Marzano D., Frankel J., Smith S.B., and Andreatta P. 2011. A simulation-based scenario to help prepare learners in the management of obstetric emergencies. *Simulation in Healthcare: Journal of The Society for Medical Simulation,* 6**,** 364-9.

Maslovitz S., Barkai G., Lessing J.B., Ziv A. and Many A. 2007. Recurrent Obstetric Management Mistakes Identified by Simulation. *Obstet Gynecol,* 109**,** 1295-1300.

Maternity Safety Thermometer 2014. PilotData Report 09/07/2014 Postpartum haemorrhage p10 www.safetythermometer.nhs.uk downloaded 31/07/2014

Mathew M., Machado L., Al-Ghabshi R., and Al Haddabi R. 2005. Fetal macrosomia. Risk factors and outcome. *Saudi Medical Journal,* 26**,** 96-100.

Mawhinney E., and Morrow J. 2011. Managing Epilepsy in Pregnancy: Prevalence of Epilepsy in Pregnancy. *Expert Review in Obsterics and Gynecology,* 6**,** 667-680.

May T. (1993). *Social Research: Issues, Methods and Process*. Buckingham. Open University Press.

McConnell J.S., Fox T. J., Jossen J.P., and Subramanian A., 2007. "About a cupful"- a prospective study into accuracy of volume estimation by medical and nursing staff. *Accid Emerg Nurs,* 15**,** 101-5.

McDonald S.J., and Middleton P. 2008. Effect of the timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database of Systematic Reviews*, Issue 2, CD004074.

McDonald S.J., Abbott J.M., and Higgins S.P. 2004 Prophylactic ergometine-oxytocin versus oxytocin for the third stage of labour. *Cochrane Database of Systematic Reviews* Issue 1. CD000201.

McFadden E., LoPresti F., Bailey L., Clarke E., and Wilkins P. 1995. Approaches to data management. *Control Clin Trials* 16(2), 30-65.

Medicines and Healthcare products Regulatory Agency. 2007. MHRA Guide to What is a Medicinal Product? (www.mhra.gov.uk/home/idcplg?ldcService=GET_FILE&ID=32803&noSaveAs=0&Rendition=WEB). HMSO. Accessed 16/06/2014.

Medicines for Human Use (Clinical Trials) Regulations, 2004. The statuary instrument which transposes the EU Directive into UK law. (www.mhra.gov.uk/home/groups/l-unit/documents/websiteresources/con2022633.pdf). Accessed 15/06/2014.

Mehrabadi A., Hutcheon J.A., Lee L., Kramer M.S., Liston R.M., and Joseph K.S. 2013. Epidemiological investigation of a temporal increase in atonic postpartum haemorrhage: a population-based retrospective cohort study. *BJOG,* 120, 853-62

Mehrabadi A., Hutcheon J.A., Lee L., Liston R.M., and Joseph K.S. 2012. Trends in postpartum hemorrhage 2000- 2009: a population-based study. *BMC Pregnancy and Childbirth,* 12, 108.

Metcalfe C., Martin R.M., Noble S., Lane J.A., Hamdy F.C., Neal D.E., and Donovan J.L. 2008. Low risk research using routinely collected identifiable health information without informed consent: eccounters with the Patient Information Advisory Group. *J Med Ethics*, 34, 37-40.

Meurier C.E. 2000. Understanding the nature of errors in nursing using a model to analyse critical incident reports of errors which had resulted in an adverse or potentially adverse event. *Journal of Advanced Nursing*. 32(1), 202-7.

Meyer M.B., Tonascia J. A. 1977. Maternal smoking, pregnancy complications, and perinatal mortality. *Am J Obstet Gynecol,* 128**,** 494-502.

Miles M.B., and Huberman A.M. 1994. *Qualitative Data Analysis: An Expanded Sourcebook*, p.288-97. Second Edition. Thousand Oaks, CA. Sage.

Miller S., Tudor C., Nyima., Thorsten v.R., Soman., Droyoung., Craig S., Le P., Wright L.L., and Varner M.W. 2007. Maternal and neonatal outcomes of hospital vaginal deliveries in Tibet. *Int J Gynecol and Obstet*, 98, 217-21.

Minkauskiene M. 2003. Incidence/prevalence of maternal morbidity- a lliterature review. Geneva Foundation for Medical Education and Research, Geneva.

Mitchell G.G., and Elbourne D.R 1993. The Salford Third Stage Trial. Oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage. *Online Journal of Current Clinical Trials,* 83.

Moir J.C. 1964. The obstetrician bids, and the uterus contracts. *BMJ* i, 1025-9.

Montan S. 2007. Increased risk in the elderly parturient. *Current Opinion in Obstetrics & Gynecology,* 19**,** 110-112.

Moor P., Rew D., Midwinter M.J., and Doughty H. 2009. Transfusion for trauma: civilian lessons form the battlefield? *Anaesthesia,* 64**,** 469-72.

Moore J., and Chandraharan E. 2010. Management of massive postpartum haemorrhage and coagulopathy. *Obstetrics, Gynaecology and Reproductive Medicine,* 20**,** 174-180.

Mori R., Tokumasu H., Pledge D., and Kenyon S. 2011. High dose versus lowdose oxytocin for augmentation of delayed labour. *Cochrane Database of Systematic Reviews,* 5 (10), DOI: 10.1002/14651858. CD007201.

Morris S., Sutton M., and Gravelle H. 2005. Inequallity and inequity in the use of health care in England: an empirical investigation. *Social Science & Medicine*, 60, 1251-66.

Mousa H. A., and Alfirevic Z. 2002. Major postpartum hemorrhage: survey of maternity units in the United Kingdom. *Acta Obstetricia et Gynecologica Scandinavica,* 81**,** 727-730.

Mousa, H. A., and Alfirevic Z. 2007. Treatment for primary postpartum haemorrhage. *Cochrane Database of Systematic Reviews*.

Mousa H.A., and Walkinshaw S. 2001. Major postpartum haemorrhage. *Current Opinion in Obstetrics and Gynecology,* 13 (6), 595-603.

MRC. 2004a. *ct-toolkit: Clinical trials route maps* [Online]. London: Medical Research Council. [Accessed 19/01/2011 2011].

MRC. 2004b. *ct-toolkit: Monitoring procedures* [Online]. London: Medical Research Council. [Accessed 19/12/2010 2010].

Mu Y.L., Wang S., Hao J., Shi M., Yelian F.D., and Wang X.T. 2011. Successful pregnanyes with uterine leimyomas and myomectomy at the timeof caesarean section. *Postgraduate Medical Journal,* 87 (1031), 601-4.

Munro J., Jokinen M., and Steen M. 2008. The Use of water in Labour and Birth. *Midwifery Practice Guideline.* Royal College of Midwives London.

Murphy C.M., Murad K., Deane R., Byrne B., Geary M.P.and McAuliffe F.M., 2009. Severe maternal morbidity for 2004-2005 in the three Dublin maternity hospitals. *European Journal of Obstetrics, Gynecology, & Reproductive Biology,* 143**,** 34-7.

Murphy D.J., Macleod M., Bahl., Goyder K., Howarth L., and Strachan B. 2008. A randomised controlled trial of routine versus restrictive use of episiotomy at operative vaginal delivery: a multicentre pilot study. *BJOG,* 115 (3), 1695-702.

Mutic S., Brame R. S., Oddiraju S., Parikh P., Westfall M.A., Hopkins M.L., Medina A.D., Danieley J.C., Michalski J.M., El Naqa I.M., Low D.A., and Wu B. 2010. Event (error and near miss) reporting and learning systems for improvement in radiation oncology. *Med Phys,* 37**,** 5027-36.

Myles M.F. 1985. *Textbook for midwives: with modern concepts of obstetric and neonatal care,* Chapter 12, 10th Edition, Edinburgh, Churchill Livingstone.

Nabukera S.K., Wingate M.S., Salihu H.M., Owen J., Swaminathan S., Alexander G.R., and Kirby R.S.. 2009.Pregnancy spacing among women delaying initiation of childbearing. *Arch Gynecol Obstet,* 279 (5), 677-84.

Naeff R.W. III., Chaunan S.P., Chevalier S.P., Roberts W.E., Meydrech E.F., and Morrison J.C. 1994. Prediction of Hemorrhage at Cesarean Delivery. *Obstet Gynecol,* 83 (6), 923- 6.

Nagahawaite N.T. and Goldenberg R. L. 2008. Poverty, Maternal Health, and Adverse Pregnancy Outcomes. *Ann N.Y Acad. Sci* 1136**,** 80-5.

Neeson J.D. and May K. A. 1986. *Comprehensive Maternity Nursing* Philedelphia, J.B.Lippincott.

Neill A-M. C., Nixon R. M. and Thornton S. 2002. A comparison of clinical assessment with utrasound in the management of secondary postpartum haemorrhage. *European Journal of Obstetrics & Gynecology and Reproductive Biology,* 104**,** 113-5.

Neilsen P.E., Golman M.B., Mann S., Shapiro D.E., Marcus R.G., Pratt S.D., Greenberg P., McNamee P., Sakisbury M., Birnbach D.J., Gluck P.A., Pearlman M.D., King H., Tornberg D.N. and Sachs B.P. 2007. Effects of teamwork training on adverse outcomes and process of care in labor and delivery: a randomized controlled trial. *Obstet Gynecol,* 109**,** 48-55.

Nelson G.S., and Birch C. 2006. Compression sutures for uterine atony and hemorrhage following cesarean delvery. *Int J Gynaecol Obstet*, 92, 248-50.

Newton M., Mosey L. M., Eglie G.E., Gifford W.B. and Hull C.T. 1961. Blood loss during and immediately after delivery. *Obstet Gynecol,* 17**,** 9-18.

NICE 2005. Intraoperative blood cell salvage in obstetrics. *Clinical Care Guideline* [IPG144], RCOG

NICE 2007. Intrapartum care: care of healthy women and their babies during chilbirth. Ed Walsh, A. London: NICE.

NICE 2008a. Induction of Labour. *Clinical Care Guideline.* RCOG.

NICE 2008b. Diabetes in pregnancy,management of diabetes form preconception to the postnatal period. *Clinical Care Guideline.* LONDON: RCOG/NICE.

NICE. 2010. Antenatal Care: Routine care for the healthy pregnant woman. *Clinical Care Guideline.* London, RCOG.

NICE 2014. Retained placenta. *NICE pathways* http://pathways.nice.org.uk/pathways/intrapartum-care Downloaded 01/07/2014

Nicholls K., A. S. 2007. Childbirth-related post-traumatic stress disorder in couples: a qualitative study. *British Journal of Health Psychology,* 12.

NIHR. 2004. *Clinical Trials Toolkit: route maps* [Online]. Leeds: National Institute for Health Research. Available: http://www.ct-toolkit.ac.uk/route_maps [Accessed 31/12/2012 2012].

Nizard J., Barrinque L., Frydman R., and Hernandez H. 2003. Fertility and pregnancy outcomes followiing hypogastric aretery ligation for severe post-partum haemorrhage. *Human Reproduction*, 18 (4), 844-8.

NMC 2012. Midwives rules and standards London: Nursing and Midwifery Council.

Noor S., Fawwad A., Sultana R., Bashir R., Qurat-ul-ain, Jalil H., Suleman N., and Khan A. 2009. Pregnancy with fibroids and its obstetric complication. *J Ayub Med Coll Abbottabad,* 21 (4), 37-40.

Nordstrom L., Fogelstam K., Fridman G., Larsson A., and Rydhstroem. 1997. Routine oxytocin in the third stage of labour: a placebo controlled randomised trial. *BJOG*, 104 (7), 781-6.

Nove A., Berrington A. and Matthews Z. 2012. Comparing the odds of postpartum haemorrhage in planned home birth against planned hospital birth: resuts of an observational study of over 500,000 maternities in the UK. *BMC Pregnancy and Childbirth*, 12, 130.

Novikova N., and Hofmeyr G.J. 2010. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews*, Issue 7 CD007872.

Nunn J.F. 1996. Ancient Eygptian Medicine p.193-5. British Museum Press, London.

O'Brien D., O'Sullivan O., Conroy R., McAuliffe F., Geary M., and Byrne B. 2010. Prediction of perpartum hysterectomy and end organ dysfunction in major obstetric haemorrhage. *Eur J Obstet Gynecol Reprod Biol,* 153 (2), 165-9.

O'Dwyer G., Mylotte M., and Sweeney M 1993. Experience of autologlous bloood transfusion in an obstetrics and gynaecology department. *BJOG,* 100**,** 571-4.

O'Neill O. 2006. Rethinking Informed Consent, Athena Lecture, Imperial College (16th May 2006)

Oakley A, Hickey D. and Rigby A.S. 1994. Love or money? Social support, class inequality and the health of women and children. *European Journal of Public Health,* 4**,** 265-73.

Odent M. 2008. A top obstetrician on why men should NEVER be at the birth of their child. *Daily Mail*.

Odent M. 2003. *Birth and breast feeding: Rediscovering the needs of women during pregnancy and childbirth.* Clairview Books, East Sussex

Odiho L. 2007. Does epidural analgesia affect the second stage of labour. *BJM*, 15 (7), 429-35.

ONS. 2011. 2011 Census: Key statistics for England and Wales, *Statistics Bulletin*, London, Office of National Statistics.

Onwere C., Gurol-Urganci I., Cromwell D.A., Mahmood T.A., Templeton A., and van der Meulen J.H. 2011. Maternal morbidity associated with placenta praevia among women who had elective caesarean section, *Eur J Obstet Gybecol & Reprod Biol,*159, 62-6.

Orji E.O., Shittu A.S., Makinde O.N. and Sule S.S. 2004. Effect of prolonged birth spacing on maternal and perinatal outcome. *East African medical journal,* 81**,** 388-91.

Oteng-Ntim E., Varma R., Croker H., Poston L., and Doyle P. 2012. Lifestyle interventions for overweight and obese pregnant women to improve pregnancy outcome: systematic review and meta-analysis. *BMC Medicine,* 10.

Otignah C.M., Dhanjal M.K., Harmsworth G., and Chard T. 2000. A retrospective comparison of water births and conventional vaginal deliveries. *Eur J Obstet Gynecol Reprod Biol,* 91, 15-20.

Oyelese Y. and Ananth C. V. 2010. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clinical Obstetrics and Gynecology,* 53**,** 147-156.

Oyelese Y. and Smullian J. C. 2006. Placenta Previa, Placenta Accreta, and Vasa Previa. *Obstet Gynaecol,* 107**,** 927- 941.

Ozdegirmenci O., Erkaya S., Yalvac S., Dilbaz B., Altinbas S., and Haberai A. 2010. Does early repair of episiotomy decrease postpartum blood loss: Arandomized controlled trial. *Journal of Maternal-Fetal andNeonatal Medicine,* 23 (4), 308-10.

Page D. 2007. Breastfeeding learning the dance of latchiing. *Journal of Human Lactation*, 23 (1), 111-2.

Paglia, M. J., Grotegut C. A., Johnson L. N., Thames B., and James A. H. 2012. Body mass index and severe postpartum hemorrhage. *Gynecologic and obstetric investigation,* 73**,** 70-4.

Pais S.O., Glickman M., Schwartz P., Pingoud E., and Berkowitz R. 1980. Embolization of Pelvic Arteries for Control of Postpartum Hemorrhage. *Obstet Gynecol*, 55 (6), 754-8.

Palmsten K., Hernandez-Diaz S., Huybrechts K.F., Williams P.L., Michels K.B., Achtyes E.D., Mogun H., and Setoguchi S. 2013. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ*, 347, f4877.

Papp Z., Toth-Pal E., Papp C., Sziller I., Gavai M., Silhavy M., and Hupuczi P. 2006. Hypogastric artery ligation for intractable pelvic hemorrhage. *Int J Gynecol Obstet*, 92 (1), 27-31.

Parazzini F., Ricci E., Cipriani S., Chiaffarino F., and Bortolus R. 2013. Temporal trends and determinants of peri[artum hysterectomy in Lombardy, Northern Italy, 1996-2010. *Arch Gynecol Obstet*, 287, 223-8.

Patel A. 2006a. *Blood Loss: accuracy of visual estimation* (ed) B-Lynch C *A Textbook of Postpartum Hemorrhage*, Sapiens Publishing.

Patel A., Goudar S. S., Geller S.E., Kodkany B.S., Edlavitch S.A., Wagh K., Patted S.S., Naik V.A., Moss N. and Derman R.J. 2006b. Drape estimation vs. visual assessment of estimating postpartum hemorrhage. *International Journal of Gynaecology & Obstetrics,* 93**,** 220-4.

Pattanittum P., Ewens M. R., Laopaiboon M., Lumbiganon P., McDonald S.J., Crowther C.A. On behalf of the SEA-ORCHID Study Group. 2008. Use of antenatal corticosteroids prior to preterm birth in four South East Asian countries within the SEA-ORCHID project. *BMC Pregnancy & Childbirth,* 8.

Pattinson R.C., and Hall M. 2003. Near misses: a useful adjunct to maternal death enquiries. *Br Med Bull,* 3 (67), 231-43.

Pattinson R.C., Buchmann E., Mantel G., Schoon M.and Rees H. 2003. Can enquiries into severe maternal morbidity act as a surrogate for maternal death enquiries? *BJOG,* 110**,** 889-93.

Pattinson R.C., Say L., Makin J.D. and Bastos M.H. 2005. Critical incident audit and feedback to improve perinatal and maternal mortality and morbidity (Review). *Cochrane Database of Systematic Reviews*. DOI: 10.1002/14651858.CD002961.pub2

Patton K., Funk D.L., McErlean M., and Bartfield J.M. 2001. Accuracy of Estimation of External Blood Loss by EMS Personnel. *J Trauma,* 50, 914.

Peacock L., and Clark V. 2011. Cell salvage in obstetrics: a review of data form the 2007 Scottish Confidential Audit of Severe Maternal Morbidity*. Int J Obstet Anesth,* 20 (2), 196-8.

Peacock J.L., and Peacock P.J. 2011 Chapter 6 Summerizing Data. Oxford Handbook of Medical Statistics. Oxford University Press, Oxford.

Peacock J.L., and Peacock P.J. 2013 Sampling strategies. p. 54-5. Oxford Handbook of Medical Statistics. Oxford University Press, Oxford.

Pennell C.E., Henderson J.J., O'Neill M.J., McCleery S., Doherty D.A., and Dickinson. 2009. Induction of labour in nulliparous women with an unfavourable cervix: a randomised controlled trial comparing double a nd single balloon catheters with PGE2 gel. *BJOG* 116, 1443-52.

Penney G., and Adamson L. 2007a. Scottish Confidential Audit of Severe Maternal Morbidity 4th Annual Report (data from 2006). SPCERH funded by Health Improvement Scotland.

Penney G., and Foy R. 2007b. Do clinical guidelines enhance safe practice in obstetrics and gynaecology? *Best Practice and Research Clinical Obstetrics and Gynaecology,* 21**,** 657-73.

Penney G., and Brace V. 2007. Near miss audit in obstetrics. *Curr Opin Obstet Gynecol,* 19, 145-50.

Perneger T. V. 1998. What's wrong with Bonferroni adjustment? *BMJ,* 316**,** 1236-8.

Phaneuf S., Rodrigues Linarea B., Tamby Raja R.L., MacKenzie I.Z., and Lopez Bernal A. 2000. Loss of myometrial oxytocin receptors during oxytocin-augmented labour. *J Reprod Fertil,* 120**,** 91-7.

Phillip H., Fletcher H., and Reid M. 2004. The impact of induced labour on postpartum blood loss. *Journal of Obsterics and Gynaecology,* 24**,** 12-15.

Platt L.D., and Druzin M.L. 2981. Acute puerperal inversion of the uterus. *Am JOG*, 141, 187-90.

POPPHI., and USAID. 20009. Saving Women's Lives: Prevention of Postpartum Hemorrhage. *POPPHI: Prevention of Postpartum Hemorrhage Initiative*

and USAID from the American people. www.pphprevention.org Accessed 27/10/2013.

Postnote 2002. Caesarean Sections. *In:* Technology. London: Parliamentary Office of Science and Technology.

Poston L., Briley A., Seed P., Kelly F., and Shennan A. 2006. Vitamin C and vitamin E in pregnant women at risk for pre-eclampsia (VIP trial): randomised placebo-controlled trial. *Lancet,* 367**,** 1145-54.

Poston L. 2012. Maternal obesity, gestational weight gain and determinants of offspring long term health. *Best Pract Res Clin Endocrinol Metab,* 26 (5), 627-39.

Practice Committee of the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine. 2004. Guidelines on the number if embryos transferred. *Fertility and sterility,* 82**,** 773-774.

Prata N., Hamza S., Bell S., Karasek D., Vahidnia F., and Holston M. 2011. Inability to predict postpartum hemorrhage: insights from Egyptian intervention data. *BMC Pregnancy and Childbirth,* 11, 97.

Prasertcharoensuk W., Swadpanich U. and Lumbiganon P. 2000. Accuracy of the blood loss estimation in the third stage of labor. *International Journal of Gynecolgy & Obstetrics,* 71**,** 69-70.

Prendiville W., Elbourne D., and McDonald S. 2000. Active versus expectant management of the third stage of labour. *Cochrane Database of Systematic Reviews 3*: CDC000007

Prendiville W.J., Elbourne D., McDonald S. 2003. Active versus expectant management of labour. *Cochrane Datbase of Systematic Reiews* Issue 3. CD000007 Oxford Update Software.

Prendiville W.J., Harding J.E., Elbourne D.R., and Stirrat G.M. 1988.The Bristol third stage trial: active versus physiological management of the third stage of labour. *BMJ*, 297 (6659), 1295-1300.

Pritchard J.A., Baldwin R. M., Dickey J.C. and Wiggins K.M. 1962. Red blood cell loss and changes in apparent blood volume during and following vaginal delivery, caesarean section and caesarean section plus hysterectomy. *AmJOG,* 84.

Protti D. 2007. Comparison of information technology in general practice in 10 countries. *Healthcare Q,* 10**,** 107-15.

Quadir Khan G., John I.S., Wani S., Doherty T., Sibai B.M. 1997. Controlled cord traction versus minimal intervention techniquea in delivery of the placenta: A randomised controlled trial. *Am J Obstet Gynecol*, 177 (4), 770-4.

Quenby S., Pierce S. J., Brigham S., and Wray S. 2004. Dysfunctional labor and myometrial lactic acidosis. *Obstet Gynaecol,* 103**,** 1344.

Rahman J., al-Suleiman S.A., and Rahman M.S. 2004. Obsteric and gynecologic complications in women with Marfan syndrome. *J Reprod Med*, 48, 723-8.

Raja U.A., McAree T., Bassett P., and Sharma S. 2012. The implications of a raised BMI: A DGH experience. *J Obstet Gynaecol,* 32, 247-51.

Ramanathan G., and Srulkumaran S. 2006. Postpartum haemorrhage. *Current Obstetrics and Gynaecology,* 16**,** 6-12.

Ramsahoye B., Davies S., Dassani H., and Pearson J.F. 1995. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review f the literature. *Haemophilia*, 1 (2), 140-4.

Raynor B.D. 2010. Special requirements of electronic medical records systems in obstetrics and gynaecology. *Obstet Gynaecol,* 116 (5), 1218.

RCM. 2012a. Evidence Based Guidelines for Midwifery-Led care in Labour: Rupturing Membranes. London: Royal College of Midwives.

RCM. 2012b.Evidence Based Guidelines for Midwifery-Led Care in Labour: suturing the perineum, London: Royal College of MIdwives.

RCM. 2008. Falling pay could hit midwife recruitment. *RCM Midwives*. www.rcm.org.uk/college/ about/media-centre/press-releases/falling-pay-could-hit-midwife-1/recruitment. (accessed 24/10/2013)

RCM. 2006. Domestic abuse: Pregnancy Birth and the Puerperium, *Position Statement 11,* RCM. London.

RCN. 2006. Female genital mutilation, London, Royal College of Nursing

RCOG 1992. Maternal mortality- the way forward. London RCOG

RCOG 2002. Maternal Morbidity and Mortality- study group statement. London: RCOG.

RCOG 2004. Antenatal Corticosteroids to Reduce Neonatal Morbidity (Green-top 7) 3rd edition. London: RCOG

RCOG. 2006. Obstetric Cholestasis. *Green-top Guideline No 43.* London: RCOG.

RCOG. 2009. Prevention and Management of Postpartum Haemorrhage *Green-top Guideline 52,* London: RCOG

RCOG. 2011a. Antepartum haemorrhage, *Green-top Guideline No 63,* London: RCOG.

RCOG. 2011b. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management, *Green-top Guideline No 27,* London: RCOG.

Read M.D., and Anderton J.M. Radioisoptope dilution technique for measurement of blood loss associated with lower segment caesarean section. *BJOG*, 84 (11), 859-61.

Report of the Caldicott Committee. 1997. Report of the review of patient-identifiable information. London: Department of Health.

Rizvi F., Mackey R., Barrett T., McKenna P. and Geary M. 2004. Successful reduction of massive postpartum haemorrhage by use of guidelines and

staff education. *BJOG: An International Journal of Obstetrics & Gynaecology,* 111**,** 495-8.

Roberts C. I., Algert C. S.and March L. M. 1994. Delayed childbearing - are there any risks? *Medical Journal of Australia,* 160**,** 539-544.

Roberts C.L., Torvalsen S., Cameron C.A. and Olive E. 2004. Delayed versus early pushing with epidural analgesia: a systematic review and meta-analysis. *BJOG,* 111**,** 1333-40.

Roberts C.L., Ford J.B., Algert C.S., Bell J.C., Simpson J.M. and Morris J.M. 2009. Trends in adverse maternal outcomes during childbirth: a population-based study of severe maternal morbidity. *BMC Pregnancy and Childbirth,* 9.

Roberts D., and Dalziel S. 2007. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane database of Systematic Reviews*, 4, DOI 10.1002/14651858. CD004454.pub2

Roberts J.M., and Cooper D.W. 2001. Pathogenesis and genetics of pre-eclampsia. *Lancet,* 357**,** 53-56.

Robertson A., Cresswell K., Takian A., Petrakaki D., Crowe S., Cornford T., Barber N., Avery A., Fernando B., Jacklin A., Presscott R., Klecun E., Paton J., Lichtnet V., Quinn C., Ali M., Morrison Z., Jani Y., Waring J., Marsden K., and Sheikh A. 2010. Implementation and adoption of nationwide electronic health records in secondary care in England: qualitative analysis of interim results from a prospective national evaluation. *BMJ,* 341, c4564, DOI 10.1136/BMJ.C4564.

Robinson H.E., O'Connell C. M., Joseph K.S. and McLeod N.L. 2005. Maternal Outcomes in Pregnancies Complicated by Obesity. *Obstet Gynecol,* 106.

Rogers C., Villar R., Pisal P., and Yearley C. 2011. Effects of Syntocinon use in active management of third stage of labour. *British Journal of Midwifery,* 19**,** 371-8.

Rogers J., Wood J., McCandish R., Ayers S., Truesdale A., and Elbourne D. 1998. Active versus expectant management of third stage of labour: the Hitchingbrooke randomised controlled trial. *Lancet,* 351 (9104), 693-9.

Rogers R., Gilson G., and Kammerer-Doak D. 1999. Epidural analgesia and third and fourth degree lacerations in nulliparas. *Obstet Gynecol*, 94, 259-62.

Romundstat L.V., Romundstas P. R., Sunde A., von During V., Skjaerveb R. and Vatten L.J. 2006. Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother. *Human Reproduction,* 21**,** 2353-8.

Ronsmans C., and Filippi V. 2004. Reviewing severe maternal morbidity: learning form the women who survive life threatening complications. In: Lewis G (ed). Beyong the Numbers. Reviewing maternal Deaths and Complications to Make Pregnancy Safer. Geneva, Switzerland. World Health Organisation, 103, 103-23.

Rosnes J.S., Sharkey M.F., Veille J.C., and Mueller-Heubach E. 1996. Gaucher's disease in pregnancy. *Obstet Gynecol Surv*, 51,549-58

Rossen J., Okland I., Nilsen O.B., and Eggebo T.M. 2010. Is there an increase of postpartum hemorrhage, and is severe hemorrhage associated with more frequent use of obstetric interventions? *Acta Obstetrica et Gynecologica Scandinavica,* 89 (10), 1248-55.

Rossi A.C., Lee R.H., and Chmail R.H. 2010. Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systemativ review. *Obstet Gynecol*, 115 (3), 637-44.

Rossi C.A., and Mullin P. 2012. The etiology of maternal mortality in developed countries: a systematic review of the literature. *Arch Gynaecol Obstet*. 285 (6), 1499- 503.

Rothman, K. J. 1990. No adjustments needed for multiple comparisons. *Epidemiology,* 1**,** 43-6.

Rothwell P.M. 2005. Treating individuals 1. External validity of randomised controlled trials "To whm do the results of this trial apply?" *Lancet*, 365, 82-93.

Rowe R.E., Magee H., Quigley M.A., Heron P., Askham J., and Brocklehurst P. 2008. Social and ethnic differences in attendance for antenatal care in England. *Public Health*, 122, 1363-72.

Rowe R.E., Garcia J., and Davidson L.L. 2004. Social and ethnic inequalities in the offer and uptake of prenatal screening and diagnosis in the UK: a systematic review. *Public Health*, 118, 177-89.

Saito K., Haruki A., Ishikawa H., Takahashi T., Nagase H., Koyama M., Endo M., and Hirahara F. 2007. Prospective study of intramuscular ergometrine compared with intrmuscular oxytocin for prevention of postpartum hemorrhage. J Obstet Gynaecol Res.

Salomon L.J., deTayrac R., Castaigne-Meary V., Audibert F., Musset D., Ciorascu R., Frydman R., and Fernandez H. 2003. Fertilty a nd pregnancy outcome following pelvic arterial embolization for severe post-partum haemorrhage. a cohort study. *Human Reproduction*, 18 (4), 849-52.

Saule I., and Hawkins N. 2012. Transfusion practice in major obstetric haemorrhage: lessons from trauma. *Int J Obstet Anesth,* 21 (1), 79-83.

Say L., Pattinson R.C., and Gulmezoglu A.M. 2004 WHO systematic review of maternal morbidity and mortality: the prevalence of severe acute maternal morbidity (near miss). *Reprod Health*, 1, 3.

Schmid B.C., Rezniczek G.A., Rolf N., Saede G., Gebauer G., and Maul H. 2013. Uterine packing with chitosan-covered gauze for control of postpartum hemorrhage. *Am J Obstet Gynecol*, 209 (225), e1-5.

Schmid B.C., Rezniczek G.A., Rolf N., and Maul H. 2012. Postpartum hemorrhage: use of combat gauze. *AmJOG,* 206 (1), e12-13.

Schorn M.N. 2010. Measurement of blood loss: review of the literature. *Journal of Midwfery & Women's Health,* 55 (1), 20-7.

Schouten F.D., Wolf H., Smit B.J., Bekedam D.J., Devos R. and Wahlen I. 2008. Maternal temperature in labour. *BJOG,* 115**,** 1131-7.

Schuitemaker N., van Roosmalen J., Dekker G., van Dongen P., van Geijn H., and Bennebroek Gravenhorst J. 1998. Confidential enquiry into maternal deaths in the Nteherlands 1983-1992. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, 79, 57-62.

Schumacher M., Zubaran M., and White G. 2008. Bringing birth related paternal depression to the fore. *Women & Birth,* 21**,** 65-70.

Scopelliti J. 2010. Benefits of an early start with EMR. The early roll-out of an EMR system was met with scepticism, but has resulted in higher performance and patient care quality. *Health Informatics Journal,* 27**,** 50-7.

Scott J.E. 2008. Peripartum Bleeding at Cesarean Delivery, Be Prepared! *Obstetrics & Gynecology,*112 (2 part 2), 417-8.

Sebire N.J., Jolly M., Harris J.P., Regan L., and Robinson S. 2001a. Is maternal underweight really a risk factor for adverse pregnancy outcome? A population-based study in London. *British Journal of Obstetrics & Gynaecology,* 108**,** 61-66.

Sebire N.J., Jolly M., Harris J., Nicolaides K.H., and Regan L. 2001b. Risk of obstetric complications in multiple pregnancies: an analysis of more than 400,000 pregnancies in the UK. *Perinatal and Neonatal Medicine,* 6**,** 89-94.

Sebire N.J., Jolly M., Harris J.P., Wadsworth J., Joffe M., Beard R.W., Regan L., and Robinson S. 2001c. Maternal obesity and pregnancy outcome: a study of 287 213 pregnancies in London. *International Journal of Obesity,* 25**,** 1175-82.

Selo-Ojeme D., Rogers C., Mohanty A., Zaid N., Villar R., and Shangaris P. 2011. Is induced labour in the nullipara associated with more maternal and perinatal morbidity? *Arch Gynecol Obstet,* 284 (2), 337-41.

Selo-Ojeme D.O., Bhattacharjee P., Izuwa-Njoku N.F and Kadir R.A. 2005. Emergency peripartum hysterectomy in a tertiary London hospital. *Arch Gynecol Obstet*, 271 (2), 154-9.

Seng J.S., Oakley D. J., Sampselle C.M., Killion C., Graham-Bermann S. and Liberzon I. 2001. Post traumatic Stress Disorder and Pregnancy Complications. *Obstet Gynecol,* 97**,** 17-22.

Sentilhes L., Descamps P., and Marpeau L. 2010a. Has B-Lynch suture hidden long-term effects? *Fertility and sterility,* 94**,** e62.

Sentilhes L., Kayem G., Ambroselli C., Provansal M., Fernandez H., Perrotin F., Winner N., Pierre F., Benachi A., Dreyfus M., Bauville, E., Mahieu-Caputo D., Marpeau L., Descamps P., Bretelle F., and Goffinet F. 2010b. Fertility and pregnancy outcomes following conservative treatment for placenta accreta. *Human reproduction,* 25**,** 2803-10.

Shah M.,and Wright J.D. 2009. Surgical Intervention in the Management of Postpartum Hemmorhage. *Seminars in Perinatology*, 33, 109-15.

Shahida S.M., Islam M.A., Begum S., Hossain M.A., and Azam M.S. 2011. Maternal outcome of grand multipara. *Mymensingh Medical Journal 20 (3), 381-5.*

Shand A.W., Bell J.C., McElduff A., Morris J., and Roberts C.L. 2008. Complications of pregnancies in women with pre-gestationaldiabetes mellitus and gestational diabetes;a population-based study in New South Wales, Australia, 1998-2002. *Diabetic Medicine,* 25 (6), 708-15.

Sheikh A., Cornfod T., Barber N., Avery A., Takian A., Lichtner V., Petrakaki D., Crowe S., Marsden K., Robertson A., Morrison Z., Kiecun E., Prescott R., Jani Y., Ficociello M., Voutsina K., Paton J., Fernando B., Jacklin A., and Cresswell K. 2011. Implementation and adoption of nationwide electronic health records in secondary care in England: final qualitative results from prospective national evaluation in "early adopter" hospitals. *BMJ,* 343, d6054. DOI: 10.1136/bmj.d6054.

Sheiner E., Sarid L., Levy A., Seidman D.S.and Hallak M. 2005. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. *Journal of Maternal-Fetal and Neonatal Medicine,* 18**,** 149-154.

Shennan A., Crawshaw S., Briley A., Hawken J., Seed P., Jones G. and Poston L. 2006. A randomised controlled trial of metronidazole for the prevention of preterm birth in women positive for cervicovaginal fetal fibronectin: the PREMET Study. *BJOG: An International Journal of Obstetrics & Gynaecology,* 113**,** 65-74.

Shennan A., and Halligan A. 1996. Blood pressure measurement in pregnancy: room for improvement. *Maternal Child Health Journal,* 21**,** 55-9.

Shevell T. and Malone F. D. 2003. Management of Obstetric Hemorrhage. *Semin Perinatol,* 27**,** 86-104.

Shevell T., Malone F. D., Vidaver J., Porter T.F., Luthy D.A., Comstock C.H., Hankins G.D., Eddleman K., Dolan S., Dugoff L., Ctaigo S., Timor I.E., Carr S.R., Wolfe H.M., Bianchi D.W. and D'Alton M.E., for the FASTER Research Consortium. 2005. Assisted Reproductive Technology and Pregnancy Outcome. *Obstetrics & Gynecology,* 106**,** 1039-45.

Sibai B.M. 2002. Chronic hypertension in pregnancy. *Management of Chronic hypertension in pregnancy,* 100.

Shields L.E., Smalarz K., Reffigee L., Mugg S., Burdumy T.J., and Propst M. 2011. Comprehensive maternal hemorrhage protocols improvepatient safety and reduce utilization of blood products, *Am JOG,* 205 (4), 368 e1-8.

Siggelkow W., Boehm D., Skala C., Grosslercher M., and Koebl H. 2008. The influence of macrosomia on the duration of labor, the mode of delivery and intrapartum complications. *Arch Gynecol Obstet,* 278 (6), 547-53.

Silow-Carroll S., Edwards J.N., and Rodin D. 2012. Using electronic health records to improve quality and efficiency: the experiences of leading hospitals. *Issue Brief,* 17, 1-40.

Sin C.H. 2005. Seeking Informed Consent: Reflections on research Practice, *Sociology*, 39(2), 277-94.

Singh K., Fong Y. F., and Arulkumaran S. 1998. Anaemia in pregnancy- a cross-sectional study in Singapore. *Eur J Clinical Nutrition,* 52**,** 65-70.

Sinha P., and Mishra M. 2012. Caesarean scar pregnancy: A precursor of placenta percreta/accreta. *Journal of Obstetrics & Gynaecology,* 32**,** 621-3.

Sluiter J.K., van der Beek A.J., and Frings-Dresen M.H.2003. Medical staff in emergency situations: severity of patients status predicts stress hormone reactivity and recovery. *Occup Environ Med*, 60 (5), 374-5.

Smellie W. A treatise on the theory and practice of midwifery: 402-4. D.Wilson London

Smith G.C.S., Cordeaux Y., White I.R., Pasupathy D., Missfelder-Lobos H., Pell J.P., Charnock-Jones D.S., and Fleming M. 2008. The effect of delaying childbirth on primary cesarean section rates. *PLoS Med,* 5 (7), e144.

Somers-Smith M. J. 1999. A place for the partner? Expectations and experiences of support during childbirth. *Midwifery,* 15**,** 101-8.

Soobrayan V. 2003. Ethics, Truth and Politics in Constructivist Qualitative Research. *Westminster Studies in Education*, 26 (2), 107-23.

Sosa C.G., Althabe F., Belizan J.M., Buekens P. 2009. Risk factors for Postpartum Hemorrhage in Vaginal Deliveries in a Latin-American Population. Obstet GYnecol, 113 (6), 1313-9.

Sonneveld S.W.and Correy J. F. 1990. Outcome of pregnancies complicated by epilepsy in Tasmania 1981-1988. *Aust NZ J Obstet Gynaecol,* 304**,** 286-9.

Spahn D.R., and Rossaint R. 2005. Coagulopathy and blood component transfusion in trauma. *British Journal of Anaesthesia,* 95**,** 130-9.

Spencer P. 1962. Controlled cord traction in management of the third stage of labour. *BMJ*,1, 1728-32

Stafford I., Dildy G.A., Clark S.L. and Belfort M.A. 2008. Visually estimated and calculated blood loss in vaginal and cesarean delivery. *Am J Obstet Gynecol,* 199**,** e1-519e7.

Stahl D.L., Groeben H., Kroepfl D., Gautam S., and Elkermann M. 2012. Development and validation of a novel tool to estimate peri-operative blood loss. *Anaesthesia,* 67, 479-86.

Stainsby D., MacLennan D., Thomas D., Isaac J., and Hamilton P.J. 2006. Guidelines on the management of massive blood loss. *British Journal of Haematology*, 135, 634-71.

Stata, version 11.2. Stata Corp, College Station, Texas, USA.

Stevens K.R. and Munoz L.R. 2004. Cigarette Smonking: Evidence to Guide Measurement. *Research in Nursing & Health,* 27, 281-92.

Stearns J. 1808. Account of the pulvis partutiens, a remedy for quickening childbirth. *Med Repository NY*, 11, 308-9.

Stearns J. 1822. Observations on the scale cornutumor ergot, with directions for its use in partuition. *Med Repository*, 5:90

Stock S.J., Ferguson E., Duffy A., Ford I., Chalmers J., and Norman J.E. 2012. Outcomes of elective induction of labour compared with expectant management: population based study. *BMJ,* 344**,** e2838.

Stones W., Lim W., Al Azzawi F., and Kelly M. 1991. An investigation of maternal morbidity with identificationof life-threatening 'near miss' episodes. *health Trends*, 23, 985-90.

Stones R.W., Paterson C.M. and Saunders N.J. StG. 1993. Risk factors for major obstetric haemorrhage. *Eur J Obstet Gynecol Reprod Biol,* 48**,** 15-18.

Su L., Chong Y., Samuel M. 2007. Oxytocin agonists for preventing postpartum haemorrhage. *Cochrane Database of Systematic Reviews,* Issue 3*,* CD005457

Sundararajan V., Reidpath D.D., and Allotey P. 2007. Ethnicity, discrimination and health outcomes: a secondary analysis of hospital data from Victoria, Australia. *Diversity in Health and Social care,* 4**,** 21-32.

Takoudes T.., Weitzen S., Slocum J., and Malee M. 2004. Risk of cesarean wound complications in diabetic gestations. *AmJOG*, 191, 958-63.

Tall G., Wise D., Grove P., and Wilkinson C. 2003. the accuracy of external blood loss estimation by ambulance and hospital personnel. *Emerg Med*, 15, 318-21.

Tata L.J., Lewis S. A., McKeever T.M., Smith C.J., Doyle P., Smeeth L., West J. and Hubbard R.B., 2007. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med,* 175**,** 991-7.

Taylor L.K., Travis S., Pym M., Olive E., and Henderson-Smart D.J. 2005. How useful are hospital morbidity data for monitoring conditions occuring in the perinatal period? *Aust NZ Obstet Gynaecol*, 45 (1), 36-41.

Taylor L.K., Simpson J.M., Roberts C.M., Olive E.C., and Henderson-Smart D.J. 2005. Risk of complications in a second pregnancy following caesarean section in the first pregnancy: a population based study. *MJA*, 183, 515-9.

Temple R. 2003. Impact of the Declaration of Helsinki on Medical Research from a Regulatory Perspective. *Address to the Scientific Session, World Medical Aassociation Generally Assembly*, September 2003, Helsinki.

The CRASH-2 Trial Collaborators. 2006. Improving the Evidence Base for Trauma Care: Progress in the International CRASH-2 Trial. *PLOS Clinical Trials*.

The European Commission in consultation with the Member States and the European Medicines Agency. 2006. The Rules Governing Medicinal Products in the European Union. (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm) Accessed 16/06/2014.

Thevakumar R.A., Valayatham V., and Bewley S. 2008. Defining obstetric terms: The need for gold standards. *Journal of Obstetrics and Gynaecology,* 28**,** 36-43.

Throckmorton T., and Etchegaray J. 2007. Factors affecting incident reporting by Registered Nursed: the relationship of perceptions of the environment for reporting errors, knowledge of the Nursing Practice Act, and demographics on intent to report errors. *Journal of PeriAnesthesia Nursing*. 22(6), 400-12.

Tighe C.M., Woloshynowych M., Brown R., Wears B., and Vincent C. 2006. Incident reporting in one UK accident and emergency department. *Accid Emerg Nurs.* 14, 27-37.

Tikkanen M., Paavonen J., Loukovaara M., and Stefanovic V. 2011. Antenatal diagnosis of placenta accreta leads to reduced blood loss. *Acta Obstet Gynecol Scand.*

Tindale J., and Hardiker N. 2012. Use of technology in childborth: 7. Electronic maternity records. *Practising Midwife,* 15 (4), 38-41.

Tindell K., Garfinkel R., Abu-Haydar E., Ahn R., Burke T. F., Conn K., and Eckardt M. 2013. Uterine balloon tamponade for the treatment of postpartum haemorrhage in resource-poor settings: a systematic review. *BJOG : an international journal of obstetrics and gynaecology,* 120**,** 5-14.

Titiz H., Wallace A ., and Voaklander D.D. 2001. Manual removal of placenta:a case control study. *Aust NZ J Obstet Gynaecol*, 41, 41-4.

Toledo P., McCarthy R.J., Burke C.A., Goetz K., Wong C.A., and Grobman W.A. 2010. The effect of web-based education on the accuracy of blood loss estimation in simulated obstetric scenarios. *AmJOG,*202 (4), 400.e1-5.

Tomson T. and Hiilesmaa V. 2007. Epilepsy in pregnancy. *BMJ,* 335, 769-73.

Tribe R.M., Crawshaw S.E., Seed P.T., Shennan A.H., and Baker P.N. 2012. Pulsatile versus continuous administration of oxytocin for induction and augmentation of labor: two randomised controlled trials. *AmJOG,* 206 (230), e1-8.

Trust For London. 2010. *London Poverty Profile* [Online]. London: Trust for London and New Policy Institute. Available: http://www.londonspovertyprofile.org.uk/about/an-overview-of-londons-borough/ Accessed 18/08/2013 2013.

Tucker M.J., Berg C. J., Callaghan W.M., and Hsia J. 2007. The Black-White Disparity In Pregnancy-Related Mortality From 5 Conditions: Differences in Prevalence and Case- Fatality Rates. *Am J Public Health,* 97**,** 247-51.

Tunis S.R., Stryer D.B., and Clancy C.M. 2003.Practical Clinical Trials. Increasing the Value of Clinicla Research for Decision Making in Cliical and Health Policy. *JAMA*, 290, 1624-32.

Uebersax J.S. 1989. Validity Inferences form Interobserver Agreement. *A Rand Note.* Santa Monica: The RAND Corporation.

UKOSS. 2013. A new national system to syuudy rare disorders of pregnancy. United Kingdom. Oxford, NPEU www.npeu.ox.ac.uk/ukoss accessed 25/08/2013.

UNICEF 2004. The State of the World's Children 2005- Childhood under threat. UNICEF. www.unicef.org.uk

UNICEF. 2008. Progress for Children: A report card on maternal mortality. New York.

Unterscheider J., McMenamin M., and Cullinane F. 2011. Rising rtaes of caesarean deliveries at full dilatation: a concerning trend, *Eur J Obstet, Gnecol Reprod Biol,* 157 (2), 141-4.

Usha Kiran T.S., Hemmadi S., Bethel J. and Evans J. 2005. Outcome of pregnancy in a woman with an increased body mass index. *BJOG,* 112**,** 768-72.

Vaid A., Dadhwal V., Mittal S., Deka D., Misra R., Sharma J.B., and Vimla N. 2009. A randomised controlled trial of prophylactic sublingual misoprostol versus intramuscular methyl-ergometrineversus intramuscular 15-methyl PGF2-alpha in active managem,ent of the third stage of labor. *Arch of Gynecol Obstet,* 280(6), 893-7.

Vais A., and Bewley S. 2006. *A Textbook of Postpartum Hemorrhage: A Comprehensive Guide to Evaluation management and surgical intervention. Chapter 37*.

van Roosmalen J., and Zworst J. 2009. Severe maternal morbidity in high income countries. *Best Practice & Research in Clinical Obstetrics & Gynaecology,* 23**,** 297-304.

Varatharajan L., Chandraharan E., Sutton J., Lowe V., and Arulkumaran S. 2011. Outcome of the management of massive postpartum hemorrhage using the algorithm "HEMOSTASIS" *Int J Gynaecol Obstet*, 113 (2), 152-4.

Vincent C., Stanhope N., and Crowley-Murphy M. 1999. Reasons for not reporting adverse incidents: an empirical study. *Journal of Evaluation in Clinical Practice*. 5 (1), 13-21.

Vitthala S., Tsoumpou I., Anjum Z.K., Aziz N.A. 2009. Use of Bakri baloon in post-partum haemorrhage; a series f 15 cases. *Aust NZ J Obstet Gynaecol*. 49, 191-4.

Volkov N., Nisenblat V., Ohel G., and Gonen R. 2007. Ehlers-Danlos Syndrome: Insights on Obstetric Aspects. *Obstet Gynecol Surv*, 62 (1), 51-5.

von Katterfeld B., Li J., McNamara B., and Langridge A.T. 2011. Obstetric profiles of foreign-born women in Western Australia using data linkage, 1998-2006. *The Aus NZ J Obs Gynae,* 51 (3), 225-32.

Walfish M., Neuman A. and Wlody D. 2009. Maternal haemorrhage. *British Journal of Anaesthesia,* 103**,** 147- 56.

Walker M.C., Murphy K. E., Pan S., Yang Q. and Wen S.W. 2004. Adverse maternal outcomes in multifetal pregnancies. *BJOG,* 111**,** 1294-6.

Walley T. 2006. Using personal health information in medical research. Overzealous interpretation of UK laws is stiffling epidemiological research. *BMJ*. 332, 130-1.

Wang B.S., Zhou L.F., Coulter D., Liang H., Zhong Y., Guo Y.N., Zhu L.P., Gao X.l., Yuan W., and Goa E.S. 2010. Effects of caesarean section on maternal health in low risk nulliparous women: a prospective matched cohort study in Shanghai, China. *BMC Pregnancy & Childbirth,* 10, 78.

Waring J.J. 2005. Beyong blalme:cutural barriers to medical incident reporting. *Social Science Medicine*. 60, 1927-35.

Watanabe T., and Matsubara S. 2010. No bleeding before, more bleeding later: the relationship between the presence of warning bleeding and the amount of bleeding during caesarean section in placenta praevia. *J Obstet Gynaecol,* 30 (8), 836.

Waterstone M., Bewley S., and Wolfe C. 2001. Incidence and predictors of severe obstetric morbidity: case-control study. *BMJ,* 322**,** 1089-93.

Waterstone M., Wolfe C., Hooper R. and Bewley S. 2003. Postnatal morbidity after childbirth and severe obstetric morbidity. *BJOG,* 110**,** 128- 133.

Webster V.J., Stewart R., and Stewart P. 2010. A survey of interventional radiology for the management of obstetric haemorrhage in the United Kingdom. *International Journal of Obstetric Anesthesia,* 19**,** 278-81.

Weeks A.D. 2008. The retained placenta. *Best practice & research. Clinical obstetrics & gynaecology,* 22**,** 1103-17.

Weeks A. 2007. Umbilical cord clamping after birth better not to rush. *BMJ*, 335, 312-3.

Wen S.W., Huang L., Liston R., Heaman M., Baskett T., Rusen I.D., Joseph K.S., and Kramer M.S., Maternal Health Study Group Canadian Perinatal Surveillance System. 2005. Severe maternal morbidity in Canada 1991-2001. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne,* 173**,** 759-64.

Werler M.M. 1997. Teratogen Update: Smoking and Reproductive Outcomes, *Teratology,* 55, 382-8.

Weston N., on behalf of RCOG. 2012. BJOG Release: Severe postpartum haemorrhage less likely with planned caesarean section, finds study. RCOG Accessed 06/08/2012

Whittle M., On behalf of the working party. 2007. Safer Childbirth: Minimum Standards for the Organisation and Delivery of Care in Labour. London: RCOG, RCM, RCOA, RCOPCH.

WHO. 1990a. Measuring reproductive morbidity. Report of a Technical Working Group: 1989 Aug 30-Sept 1st Geneva: WHO.

WHO. 1990b. The Prevention and Management of Postpartum Haemorrhage. Report of a Technical Working Group, Geneva, 3–6 July, 1989. Unpublished document. WHO/ MCH/90.7. Geneva: World Health Organization, 1990. Geneva 3-6July 1989. Unpublished document.: World Health Organisation.

WHO 2000. Managing complications in Pregnancy and Childbirth. World Health Organisation. Geneva.

WHO. 2004. Maternal Mortality in 2000: Estimates developed by the WHO, UNICEF and UNFPA. World Health Organisation. Geneva.

WHO. 2006a. Female genital mutilation and obstetric outcome: WHO collaborative prospective study in six African countries. *Lancet,* 367**,** 1835-41.

WHO. 2006b. Department for Making Pregnancy Safer, WHO Recommendations for Preventing Postpartum haemorrhage: World Health Organisation. Geneva

WHO. 2007a. *List of Official ICD-10 Updates* [Online]. Geneva: WHO. Available: http://www.who.int/classifications/icd/icd10updates/en/index.html [Accessed 31/08/2008 2009].

WHO 2007b. Saving women's lives: evidence-based recommendations for the prevention of postpartum haemorrhage. *Bulletin of the World Health Organization,* 85**,** 322-323.

WHO 2008. Worldwide prevalence of Anaemia 1993-2005. *In:* De Benoist B., M. E., Cogswell M., (ed.). Geneva: World Health Organisation.

WHO. 2009a. *10 facts about breast feeding* [Online]. Geneva: WHO. [Accessed 8th June 2010].

WHO 2009b. WHO guidelines for the management of postpartum haemorrhage and retained placenta.

WHO. 2012a. *Fact Sheet No. 241. Female genital mutilation* [Online]. Geneva: WHO. Available: http://www.who.int/mediacentre/factsheets/fs241/en [Accessed 02 January 2013 2013].

WHO 2012b. WHO recommendations for the prevention and treatment of postpartum haemorrhage. *In:* Gulmezoglu, A. M., Souza J.P. (ed.). Geneva: World Health Organisation.

WHO. 2013. *International Classification of Diseases (ICD)* [Online]. WHO. Available: http://www.who.int/classifications/icd/en/ [Accessed 14/08/2013 2013].

Wickham S. 2010. Classification of urgency of Caesarean section- a continuum of risk. *Essentially MIDIRS,* 1 (3), 27-30.

Widmer M., Blum J., Hofmeyr G. J., Carroli G., Abdel-Aleem H., Lumbiganon P., Nguyen T. N., Wojdyla D., Thinkhamrop J., Singata M., Mignini L. E., Abdel-Aleem M. A., Tran S. T., and Winikoff B. 2010. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum

haemorrhage: a multicentre, double-blind randomised trial. *Lancet,* 375**,** 1808-13.

Wikkelsoe A.J., Afshari A., Stensballe J., Langhoff-Roos J., Albrechtsen C., Ekelund K., Hanke G., Sharif H.F., Mitchell A.U., Svare J., Troelstrup A., Pedesen L.M., Lauenborg J., Madsen M.G., Bodker B., and Moller A.M. 2012. The FIB-PPH trial: fibrinogen concentrate as initial treatment for postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials*. 13, 110.

Wiles R., Heath S., Crow G., and Charles V. 2005. *Informed Consent in Social Research: a literature review*. Southampton ESRC National Centre for Research Methods.

Williams C. 2007. Arbitrary time limits for the second stage of labour- do they disempower women from achieving normal birth? A literature review.*MIDIRS Midwifery Digest,* 17 (4), 527-33.

Williams F.L.R., Du V Florey C., Ogstin S.A., Patel N.B., Howie P.W.and Tindall V.R. 1998. UK study of intrapartum care for low risk primigravidas: a survey of interventions. *J Epidemiol Community Health,* 52**,** 494-500.

Winter C., MacFarlane A., Deneux-Tharaux C., Zhang W.H., Alexander S., Brocklehurst P., Bouvier-Colle MH., Prendiville W., Cararach V., Van Roosemalen J., Berbik I., Klein M., Ayres-de-Campos D., Erkkola R., Chiechi L.M., Langhoff-Roos J., Stray-Pedersen B.and Troeger C. 2007. Variations in policies for management of the third stage of labour and the immediate management of postpartum haemorrhage in Europe. *BJOG: An International Journal of Obstetrics & Gynaecology,* 114**,** 845-854.

Wise A. and Clark V. 2008. Strategies to manage major obstetric haemorrhage. *Current Opinion in Anesthesiology,* 21**,** 281-287.

Wise L.A., Palmer J.R., Crozier Y.C., Hunt M.O., Stweart E.A. and Rosenberg L. 2007. Perceived racial discrimination and risk of uterine leiomyomata. *Epidemiology,* 18(6), 747-57.

Woloshynowych M., Rogers S., Taylor-Adams S., and Vincent C. 2005. The investigation and analysis of critical incidents and adverse events in healthcare, *Health Technology Assessment*. 9 (19).

Wood S., Cooper S., and Ross S. 2014. Does induction of labour increase the risk of caesarean section? A systematic review and meta-analysis of trials iin women with intact membranes. *BJOG*, 121, 674-85.

Wuntakai R., Kaler M., Hollingworth T. 2013. Women with high BMI: should they be managed differently due to antagonising action of leptin in labour? *Medical Hypotheses,* 80(6), 767-8.

Yamani Zamzami T.Y. 2003. Indications of emergency peripartum hysterectomy: review of 17 cases. *Arch Gynecol Obstet*, 268 (3), 131-5.

Yogev Y., Melamed N., Bardin R., Tenebaum-Gavish K., Ben-Shitrit G., and Ben-Haroush A. 2010. Pregnancy outcome at extremely advanced maternal age. *AmJOG,* 203 (6), 558.e1-7.

Yoong W., Massiah N.and Oluwu A. 2006. Obstetric hysterectomy: changing trends over 20 years in a multiethnic high risk population. *Arch Gynecol Obstet,* 274**,** 37-40.

Young B.C., Levine R.J., and Karumanchi S.A. 2010. Pathogenesis of preeclampsia. *Annual Review of Pathology,* 5, 173-92.

Young B.K and Gorstein F. 1968. Maternal osteogenesis imperfecta. *Obstet Gynecol* 31, 461-70.

Yucel O., Ozdemir I., Yucel N., and Somunkiran A. 2006. Emergency peripartum hysterecromy: a 9 year review. *Arch Gynecol Obstet*, 274 (2), 84-7.

Zdravkovic T., Genbacev O., McMaster M.T., and Fisher S.J. 2005. The Adverse Effects of Maternal Smoking on the Human Placenta: A Review. *Placenta,* 26 Suppl A, Trophoblast Research Volume 9.

Zhang J., Bricker L., Wray S., and Quenby S. 2007. Poor uterine contractility in obese women. *BJOG: An International Journal of Obstetrics & Gynaecology,* 114**,** 343-348.

Zhang W., Deneux- Tharaux C., Brocklehurst P., Juszczak E., Joslin M.and Alexander S. 2010. Effect of a collector bag for measurement of postpartum blood loss after vaginal delivery: cluster randomised trial in 13 European countries. *BMJ: British Medical Journal (Overseas & Retired Doctors Edition),* 340**,** c293-c293.

Zhang W-H, Alexander S., Bouvier_Colle M-H., MacFarlane A., the MOMS-B Group. 2005. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for sever maternal morbidity in a European population-based study: the MOMS-B survey. *BJOG,* 112**,** 89-96.

Zwart J. J., Richters J.M., Ory F., De Vries J.I., Bloemenkamp K.W. and van Roosmalen J. 2008. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. *BJOG,* 115**,** 842-50.

Zwart J.J. 2009. Safe Motherhood: SEvere maternal morbidity in the Netherlands, the LEMMoN study. *PhD Thesis*, University of Leiden, supervisor: van Roosemalen J.

Zwart J.J.,Dijk P.D., van Roosemalen J. 2010. Peripartum hysterectomy and arterial embolization for major obstetric hemorrhage: a 2 year nationwide cohort study in the Netherlands. *Am J Obstet Gynecol*, 202, 150, e1-7.